

FOOD INFECTIONS AND FOOD INTOXICATIONS

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PREFACE

The material that forms the basis for a detailed discussion of *Food Infections and Food Intoxications* is scattered through many journals and consists of the clinical and experimental observations of a large number of individuals. In any attempt to bring this information together the writer is therefore confronted with the possibility of making errors of omission. In the present instance this danger is fully recognized and wherever such errors may occur they are due to oversight and not intent.

The treatment of the subject matter of food poisoning, as presented in this book, follows a plan designed to satisfy the interest of several groups of individuals. Wherever possible the phases of etiology, symptomatology, diagnosis, treatment and prophylaxis are presented in detail. Throughout the book an attempt is made at a fair evaluation of the experimental evidence in each type of food poisoning. The result is that in certain instances the discussion as presented is rather tentative but where this is the case a perusal of the text will indicate that our present knowledge of that particular subject is in such a state of flux as not to admit any degree of dogmatism.

In general, an attempt has been made to distinctly separate the two subjects of Food Infection and Food Intoxication and for the most part we believe that the line may be sharply drawn. However, there does seem to be a certain amount of unavoidable overlapping as, for example, in the inclusion of the subject of Paratyphoid Infections in Part I, under Food Infection, and Botulism in Part II under Food Intoxication, as in the one case it is indubitably true that there are outbreaks in which the paratyphoid organisms do their work through the agency of soluble extracellular toxins while in the case of botulism it is problematical at present as to whether there may not be in-

stances in which there is an alimentary infection as well as an intoxication.

The author makes little claim to originality of content since most of the facts presented have been previously recorded in the scientific literature. For the collection of these facts from text-books, standard works of references, and from a comprehensive review of the literature in many scientific journals and for their evaluation—except as may be indicated in the text—the author assumes full responsibility. In the treatment of every subject, however, an effort has been made to incorporate the latest scientific thought.

Throughout the work wherever statements are made referring to the report or investigation of any author an effort has been made to give credit where due and these references are cited at the end of each chapter.

For many helpful suggestions and criticisms offered in the course of the preparation of the manuscript the author is obligated to his associates Dr. W. W. Ford, Dr. W. W. Cort, the late Dr. P. D. Meader, Dr. W. A. Feirer and to numerous others who have been kind enough to read and criticise portions of the text. In particular it is a pleasure to acknowledge the assistance of Dr. Norman R. Stoll in the preparation of Part III.

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S. R. D.

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PART I
INFECTIONS FROM FOOD



CHAPTER I

Introduction and definition of the subject. Food as a chance vehicle for the transmission of the etiological agent of disease. The ptomain theory of food poisoning. The bacterial theory of food poisoning.

INTRODUCTION

Transmission of the etiological agent of disease sometimes takes place directly from one individual to another. More often it takes place through some intermediate agent and food frequently serves in this capacity. In many instances food merely acts as the vehicle by which the infectious agent or toxic material is disseminated but in a number of diseases food plays an essential rôle in the transmission of the etiological agent, since in these diseases it is practically *only* through food that the causative agent is spread.

To illustrate this point the diseases diphtheria, cholera, botulism and trichinosis may be considered. *Bacillus diphtheriae*, for example, is sometimes carried by milk, as Bowhill, Eyre, and Dean and Todd have isolated it from market milk, but this is not the usual means by which it is spread. Cholera is also sometimes disseminated by food stuffs as Woodruff, Heiser and others have shown, but its usual mode of spread is by other means. On the other hand the only way in which cases of botulism ever occur in man is through the ingestion of the toxin of *Bacillus botulinus* in a food-stuff in which it has been elaborated. The instances in which this has been the case have been numerous of recent years and are illustrated by outbreaks reported by Nevin, Thom, Edmondson and Giltner, and Dickson. Likewise, infection in man by the trichina worm, *Trichinella spiralis*, can only take place through eating meat, usually pork, in which the larval stage of the parasite is encysted. Thus it may be considered that transmission of the infection is obligate by means of food.

In the chapters that follow no attempt is made to discuss the question of infectious disease as it may be caused by the chance consumption of any food-stuff which has been inadvertently subjected to infection with pathogenic bacteria. Neither is adulteration of food with chemicals or metallic poisons, in the process of manufacture, pertinent to the subject as this is usually a matter of chance. Nor is it proposed to deal with those diseases due to the consumption of foods for which individuals happen to exhibit symptoms of hypersensitivity or diseases due to habitual use of food from which one or another of the food accessory factors—the vitamins—is absent.

With this limitation of the subject in mind an effort will be made to present the evidence relative to food poisonings, due to infection or intoxication, in those diseases in which transmission of the infectious or toxic substance takes place, as a rule, *only* through the medium of food. Acquisition of infection with the bovine type of the tubercle bacillus from milk or of the broad tapeworm from infested fish illustrate the point.

Such an arbitrary limitation of the discussion may result in the omission of certain subjects which it would seem should be included. For example, nowhere in the text is there any discussion of ptomain poisoning except in the brief historical account which follows. The reason for this lies in the fact that at present there appears no justification for the retention of this expression, as the more recent investigations of illnesses in which ptomains have been held to be the cause have tended to show specific microorganisms or their toxic products as responsible.

THE PTOMAIN THEORY OF FOOD POISONING

At the present time the theory that ptomains cause food poisoning has been widely discarded but a brief historical account of the development of the ptomain or chemical theory of food poisoning is given in the paragraphs that follow. This

is necessary as providing a background for the modern conception of this subject.

Albert von Haller probably made the original scientific observations relating to the effect of decomposed protein substances upon experimental animals. His results indicated that aqueous extracts of putrid meats, when introduced into the circulation of animals, often led to symptoms of distress and frequently to death. These findings were repeated by others. From these observations the idea developed that food poisoning, especially of the type involving poisoning from spoiled meats, was in some way linked up with the production of poisonous products in the process of decomposition. This conclusion naturally antedated the period in which light was thrown on the nature of the substances involved.

In 1856 Panum first showed that the poisonous substances present in decomposing flesh could be extracted with water, that they gave definite chemical reactions, and were thermostabile. Subsequently other investigators, notably Bergmann and Schmiedeberg, obtained toxic substances of considerable potency from decomposed yeast and blood. The nature of the toxic bodies still remained unexplained, but the term "Sepsin" was coined to describe them.

Following these discoveries there ensued a period during which similar bodies were demonstrated in the watery extracts of a variety of substances and Selmi introduced the name "ptomain" for the whole group of poisonous bodies formed by the action of bacteria on animal matter. All the ptomains were of a basic nature chemically and possessed alkaloidal properties. But that such toxic bodies are not necessarily of animal origin is well known as some are found in vegetable matter. Therefore the use of the term "animal alkaloid," as it has been employed to denote the substances referred to by Selmi as ptomains is a mistake. This expression might better be used to denote the leucomaines—those bodies of a chemically basic nature which are formed during tissue metabolism in the body.

Contemporarily with Nencki, Brieger, Ladenberg, Vaughan and Novy and others were successful in the isolation and chemical investigation of numerous other ptomaines. These ptomaines were all extremely toxic when injected into the circulation of animals, and inasmuch as most of them were obtained from decomposing flesh, it was only natural that their presence in meat should be held to account for at least a large part of the indispositions attributed to the ingestion of such material. This, then, was the basis for the development of the chemical or ptomaine theory of food poisoning.

THE BACTERIAL THEORY OF FOOD POISONING

During the latter part of the period in which the ptomaine theory was being formulated, evidence had begun to accumulate which cast some doubt upon the validity of this assumption and which laid the foundation for our modern ideas as to the etiology of food poisoning.

In 1876—the year in which Nencki isolated the first ptomaine—and in the years immediately following, Bollinger directed the attention of clinicians and investigators to the close relationship between cases of food poisoning in man and disease in the animals from which the food-stuff came.

These conclusions were based entirely upon objective grounds and no definite evidence tending to show the connection between bacterial disease in the animal and disease in man was forthcoming until about 1880, when Klein investigated an epidemic due to the consumption of infected pork products. Even then definite proof was not presented, as the organism involved was not isolated, and really the first milestone in establishing the bacterial theory of food poisoning was not passed until the classical investigation of Gaertner, in 1888, and his isolation of *Bacillus enteritidis* from a fatal case of meat poisoning in man as well as from the organs of the animal from which the meat came. Thus was doubt first definitely thrown upon the chemical theory of food poisoning and the fact established that in certain cases the illness might be due to in-

fection of the individual and not alone to the action of chemical substances having the composition of ptomaines. Closely following this observation came the researches of van Ermengem, who proved that not only might *Bacillus enteritidis* be involved as an infecting agent, but that another organism—*Bacillus botulinus*—might cause illness as the result of its growth and elaboration of an extracellular toxin in the food.

Since these reports, which first directed attention to the possibility that bacteria might be the etiological agents in causing illness in man in cases that had previously been regarded as ptomaine poisoning, the bacteriological investigations of many workers have widened our field of knowledge and shown that a variety of bacterial species are capable of growing in food-stuffs under widely different conditions, and that they must be held accountable for many, if not nearly all, cases of food poisoning formerly attributed to ptomaines. In fact, at the present time improved methods of detection are more and more frequently indicating that *infection of food* is responsible for illness in those who consume it. It thus seems not at all improbable that practically all food poisoning, in which illness is not induced by a hypersensitiveness of the individual or by a metallic poison, or in which an alkaloid of vegetable origin is not involved, is due to infection.

There are still many unexplained cases of illness attributed to foods, but whenever bacteria or their toxins are sought for by the latest technique, in the majority of instances one or the other, and in some cases both, can be demonstrated. It is for this reason that investigators are now leaning toward the belief that the old ptomaine theory of food poisoning is untenable and that the real cause must be sought in the presence of pathogenic bacteria or their products in the food in question.

CHAPTER II

PARATYPHOID INFECTIONS FROM FOOD

Introduction. Organisms involved. Foods involved, taste, odor, appearance. Mortality rate. Sources of the food infection. Possibility of intoxication. Symptoms and illustrative outbreaks. Pathology. Diagnosis. Bacteriological examination. Treatment.

INTRODUCTION

At the present time there is a growing tendency to limit the term "food poisoning" to those outbreaks of gastro-intestinal disturbance caused by foods infected with the organisms of the paratyphoid-enteritidis group, or with other bacteria. Whether these disturbances are always due to a true infection of the alimentary tract by these bacteria, or whether, in some instances, they may be attributed to the absorption of toxins produced by these organisms in the food, cannot be decided at this point because the evidence appears to be more or less contradictory. Suffice it to say, however, that the modern conception is quite distinct from that of the earlier physiological chemists, who held that food poisoning was due to the presence in the food of substances known as ptomaines. This term, which was introduced by Selmi about 1850, soon came to be applied to the whole group of basic substances, having alkaloidal properties, which were obtained from decomposing proteins and which were highly toxic to animals, when injected. For this reason, clinicians quite naturally came to designate the majority of cases of gastro-enteritis as ptomaine poisoning. In the light of our present knowledge, as will be made clear later, there can be no justification for the continued use of this term, although it must be admitted that in popular estimation, as well as in medical publications, the use of the expression is apparently prevalent.

Really the first step toward the development of the modern notion as to the cause of food poisoning, was taken by Gaertner, in 1888, when he isolated *Bacillus enteritidis* at autopsy from a fatal case of what might have been termed ptomaine poisoning. At the same time he succeeded in recovering this organism from the organs of the cow from which the meat was obtained. This animal had been killed because of severe enteritis but its flesh had been eaten nevertheless. Since that time, this organism or others closely allied to it, has been isolated in the course of the investigation of a great many outbreaks and the etiological relationship firmly established. In fact, it seems evident that food poisoning of bacterial origin is very largely due to the bacteria comprising the paratyphoid-enteritidis group, and that only occasionally are other bacteria etiologically concerned.

Another early investigator to whom we are deeply indebted as aiding in the establishment of our present conception of the cause of food poisoning of this particular type, is van Ermengem, although he is better known for his work on food intoxication due to *Bacillus botulinus*.

THE ORGANISMS INVOLVED AS THE ETIOLOGICAL AGENTS IN FOOD POISONING

For the most part there is ample evidence at the present time to incriminate the various members of the paratyphoid-enteritidis group, although it must be borne in mind that occasionally other bacteria are involved in the production of food poisoning of this type. These organisms form an intermediate group of the intestinal bacteria between *Bacillus typhosus* on the one hand, and *Bacillus coli* on the other. In fact, by some writers it is referred to as the "intermediate group."

As a whole, the various members of the group have numerous characteristics in common. All of the organisms are short, non spore-forming bacilli, that exhibit a Gram-negative staining reaction, do not liquify gelatin, and are actively motile.

Grown in milk, they at first produce acid but later reversion takes place with alkali production. Their most characteristic reaction is observed in carbohydrate media however, and one of their differential features is that they do not attack either lactose or saccharose, while in glucose and mannite, both acid and gas are produced.

Of recent years there has developed a tendency to subdivide the group by means of extensive fermentation reactions, in various carbohydrate media, and on the basis of serological reactions, as has been done by Savage in England and Krumwiede in the United States. As a result, the characteristics of the group have been defined as in general quite definite and well marked, although occasionally some peculiarities are met with in individual strains.

Most prominent among the bacilli of the group are *Bacillus paratyphosus* A; *Bacillus paratyphosus* B; *Bacillus enteritidis*; *Bacillus suis*; *Bacillus typhi murium*; and *Bacillus pestis cariae*, as all of these have been implicated numerous times in outbreaks of gastro-enteritis.

FOODS INVOLVED IN FOOD POISONING, TASTE, ODOR, APPEARANCE

Various authors have reported that the evidence tended to incriminate one type of food more often than another in the production of food poisoning. Thus, Rosenau (1) reports that meat foods are most often involved, hence the not infrequent use of the term "meat poisoning" to describe these cases. On the whole, however, it would appear unwise to try to limit our ideas as to what food stuffs may be the vector of infection, as in different epidemics, beef, pork, milk, milk products, eggs, ice cream, pudding, and salad have been shown to carry the infection. As to the relative frequency with which different foods are involved Savage (2) has reported that in England non-flesh food acted as the vehicle of infection 21 times, milk 1, cream 1, ice cream 6, potatoes 2, pineapple jelly 1, canned peaches 1, rice cooked in fat 1, and meat foods 90 times or in

68 per cent of the outbreaks. On the continent other investigators have estimated that foods containing the meat of cattle or pigs have been responsible for about 61 per cent of the outbreaks.

As regards the taste, odor, appearance or texture of the food causing this type of poisoning, there is some difference of opinion. In some epidemics and in some of the experimental work in which food materials have been inoculated with the different members of the paratyphoid-enteritidis group, some of the foods have been observed to have an unusual, peculiar, or "off" odor, taste, or appearance, while in others there has been no change whatever. As an illustration of the type of outbreak in which the food material was unchanged, we may recall the classic epidemic in Ghent investigated by van Ermengem. In this instance meat was the food implicated but the meat inspector was so sure that the meat—which had passed his scrutiny—was perfectly normal, and, therefore, could not have been the cause of the epidemic, that he ate several pieces of it himself in order to prove his point. Subsequently, he developed severe cholera-like symptoms and five days later died. *Bacillus enteritidis* was recovered post mortem.

In the "meat poisoning" outbreak at Frankenhausen during which Gaertner (3) made the original isolation of *Bacillus enteritidis*, the appearance of the meat was also stated to be normal and Kaensche (4) reported an extensive outbreak at Breslau attributed to the consumption of chopped meat that was normal in color, odor, and consistency. Bowes and Ashton (5) reporting an epidemic due to the contamination of veal pies with *Bacillus enteritidis* say, "practically no one complained of the taste or appearance of the pies, which had no odor whatever." Williams (6) also reports an outbreak attributed to the consumption of pork pies infected with *Bacillus paratyphosus* B in which "no person complained of the pies at the time of eating." Other instances in which there was no evident sign of spoilage have been reported by Barker (7) Curschmann (8) and McWeeney (9).

In the above reports the food poisoning was due to the infection of a food substance containing meat or meat products in every instance. It is not to be concluded, however, that meat always acts as the vehicle of infection, as reports of similar epidemics have been made by Vagedes (10), Bernstein and Fish (11) and Sewell, Smith and Priestly (12) in which apple pie, pie dough, and canned milk were eaten. Geiger (13) has also reported that in nine outbreaks in which the causative organism was identified, the suspected food had no abnormal odor, taste, or change in texture. On the other hand, it is to be noted that in some instances, at least, the organoleptic test might have directed attention to the condition of the food as Rosenau and Weiss (14) have reported an outbreak in which some of the victims remarked on its "off" taste.

In experimental investigations involving the inoculation of various food-stuffs with the bacteria of this group, extremely varied results have been obtained. Thus, Koser (15) inoculated corned beef, Hamburger steak, canned salmon, peas, corn, spinach, tomatoes, evaporated milk, and sauerkraut, in an effort to determine the ability of these organisms to develop and spread in such material, and also in order to observe changes brought about by their growth. Employing *Bacillus enteritidis* and strains of *Bacillus paratyphosus* B it was found that multiplication took place in all the foods except in the very acid sauerkraut. At a favorable temperature, approximately blood heat, there was a remarkable growth in twenty-four to forty-eight hours, after which there was an almost abrupt decline in the number of viable organisms, especially in those foods in which the metabolic activities of the bacteria increased the acidity. In the course of these experiments it was a regular observation that there was no visible evidence of growth except in the case of peas in which a thin, friable surface scum appeared together with some gas formation. In the corn some gas was produced and in the evaporated milk a soft clot was formed, but in all these cases the condition might easily have escaped the attention of a busy chef.

or housewife, particularly as in no case was there the slightest odor or change in the physical condition of the food. Similar results have, in general, been obtained by Geiger, Davis, and Benson (16) in experimental inoculations of peas, corn, ripe olives, spinach, potted ham, salmon, evaporated milk, corned beef, peaches, and blackberry jam, with strains of *Bacillus paratyphosus* A, B, and C, *Bacillus enteritidis* and *Bacillus proteus vulgaris*. Only occasionally were changes in texture and odor of the food observed or alterations in the appearance of the container noted that might perhaps have caused the food to be discarded. For example, there was gas production in the cans of salmon, peas, corn, and potted ham, which caused them to swell and this, of course, would be regarded with suspicion by anyone using them. In no case were there noticeable changes in the appearance of the containers or their contents when inoculated with *Bacillus enteritidis*.

From these results it becomes clear that the organisms of the paratyphoid-enteritides group that have been most frequently responsible for food poisoning are able to multiply rapidly in, and spread more or less throughout a food mass. Furthermore, it seems that the changes brought about in the food are rarely so marked as to be readily detected. Certainly, under ordinary conditions of food preparation and storage in an open dish, such a thing as gas production would usually escape detection and the alteration of taste, odor, or texture is such a variable factor that no dependence can be placed upon it to indicate contamination.

MORTALITY RATE IN PARATYPHOID INFECTIONS FROM FOOD

When compared with the mortality rate in botulism or food intoxication, the rate in epidemics of paratyphoid infections from food does not appear very high as the average is between 1 and 2 per cent, while in botulism it is between 60 and 70 per cent. In different outbreaks the rate varies more or less but seldom exceeds 4 per cent.

Savage (2) reports that in 112 outbreaks in England, in-

volving 6,190 cases, there were 94 deaths, or a fatality rate of 1.5 per cent. Mayer (17) reviewing 77 outbreaks in Germany, comprising approximately 4,000 cases, reports 40 deaths and fixes the case mortality at 1 per cent, while Geiger (13) reports that in 705 epidemics in the United States, there were 5,038 cases with 255 fatalities or a death rate of 4.1 per cent. From this estimate it would appear that the death rate was a little higher in the United States than in Europe. Whether this apparent relationship will continue to hold over a long period of time remains to be seen but it is interesting to note here that the figures seem to show an increasing mortality rate in America. Thus, in 1910, Geiger reported that there were 157 deaths from food poisoning while in 1920 there were 957.

SOURCES FROM WHICH THE FOOD IS INFECTED

An examination of the literature soon leads one to the conclusion that in the majority of instances the inquiry as to the origin of any specific outbreak has not been pushed beyond the point of establishing the fact that some one or another of the paratyphoid organisms was present in the suspected food. As Savage says, "it is unfortunate that so many of the British recorded outbreaks are lacking in information in regard to the paths of infection. Many of the recorders of these outbreaks seem to have deemed it sufficient to prove the possibility of excretal contamination of the food material in question."

The importance of bridging the gaps in our knowledge as to the occurrence of *specific* organisms in food poisoning outbreaks becomes obvious if we are to discard altogether, or even in the majority of cases, the possibility that the illness may be due to intoxication resulting from putrefactive changes, brought about in the food as the result of mass infection with any of the large group of ordinary excremental bacteria. Fortunately, the evidence as to the source of the infecting organisms is slowly accumulating, with the result that even now it is possible to say that in some cases, at least, it is due to the use of meat or meat products derived from an animal itself.

infected with the specific organism, because it is a well established fact that *Bacillus enteritidis* and its congeners is pathogenic for some of our food animals as well as for man. Thus, cattle suffering from puerperal fever, septicemia, septic pyemia, diarrhea, and local suppurations may furnish meat that contains ante-mortem, the organisms of the Gaertner group. That such meat presents no warning signs of infection is well illustrated in the case of the Ghent inspector cited above. Further, Savage (18) has reported two outbreaks in England in which it was certain that the animal from which the meat came, was diseased before it was killed, while in the same report he states that due to better systems of meat inspection on the continent, it has been established that in 50 per cent of the German and Belgian outbreaks the meat was derived from diseased animals.

The evidence in other outbreaks points to the infection of meat from healthy animals subsequent to slaughter. Such infection, of course, might come about through the agency of the hands or instruments of the butcher who had previously dressed an animal that was diseased, or from a human carrier.

In such clear cut instances as the above, the source of the infection is established without difficulty but in the majority of outbreaks more obscure sources must be sought for and this necessitates taking into account such possibilities as infection of the food by human, active, or carrier cases. In this connection it is important to note the difference in the point of view of the English and at least some of the German investigators. In England it is maintained that all cases of food poisoning that can be traced to human carriers are really cases of paratyphoid fever, whereas some German writers regarding *Bacillus paratyphosus* B as identical with *Bacillus suispestifer*—and finding the latter in some normal, healthy, human intestines—affirm that it may thus readily be the source of food poisoning. There is also the possibility that food may at times become infected from the droppings of rats and mice

that have ample opportunity of coming in contact with it in the home, store, refrigerator plant, abattoir, or in transit on the railroad or vessel. That this avenue of infection is not one to be overlooked in our consideration is indicated from the investigation of Zwick and Weichel (19) who found 28 carriers of paratyphoid group organisms in the course of examining 177 mice. Heuser (20) also reported finding *Bacillus enteritidis* and *Bacillus paratyphosus* B in mice, while Savage and Read (21) isolated *Bacillus enteritidis* from the intestines of 5 of 41 rats examined. These findings have received experimental confirmation from the work of Petri and O'Brien (22) who succeeded in producing the carrier condition in laboratory animals. Finally, the possibility that food may become infected through the use of rat virus remains to be considered. That such material really has been the source of human infection appears clear from the reports of Collingridge (23) and Schibayama (24). The very wide use of such viruses together with the fact that they have actually been the source of fatalities in man sufficiently emphasizes the importance of this potential source of infection.

POSSIBILITY OF INTOXICATION FROM FOOD INFECTED WITH PARATYPHOID GROUP BACILLI

From the preceding discussion it is clear that in many cases of food poisoning there is a real infection of the intestinal tract, by one or another member of the paratyphoid-enteritidis group of bacteria, that has been introduced with the food. On the basis of these observations the present tendency to consider all food poisoning of this type as a real infection has developed, but in accepting this premise care must be exercised against overlooking other possible explanations of the condition. Thus it would hardly seem justifiable to discard altogether the experience of the great majority of people who have been made violently ill, at one time or another, by some food, under conditions that almost certainly exclude the possibility of real intestinal infection. In seeking an explanation for such cases it

is neither logical nor scientific to exclude, offhand, the possibility that at least some of these gastro-intestinal disturbances may be due to the absorption of thermostable toxic products, produced as the result of the earlier development of the organisms of the paratyphoid group in the food.

The data now at hand relative to the elaboration of toxic substances by these organisms in food hardly seems to justify the statement by Rosenau (1) that *Bacillus enteritidis* does not produce toxic or poisonous substances in food, but infects the body in the same way as *Bacillus typhosus*, causing fever and tissue injury. On the contrary, Geiger (16) makes the statement that food contaminated with organisms of the paratyphoid group "has produced symptoms of acute intoxication as evidenced by the short incubation period and the usual lack of continued fever or other form of illness." However, he continues to say that in the investigations in the United States thus far, no such filterable toxic substances have been demonstrated in the causative foods in outbreaks of food poisoning from which organisms of the paratyphoid-enteritidis group have been recovered.

The actual production of soluble toxin, under experimental conditions, by different members of the paratyphoid group, has been demonstrated repeatedly by numerous investigators. But there is considerable variation in this respect among different strains, and even in the individual strains, from time to time, under different conditions.

In the case of *Bacillus paratyphosus* B Trautmann (25) and Uhlenhuth (26) were the first to report the production of soluble toxins by this organism, while Cathcart (27) demonstrated the thermostability of the poisonous substances from autolyzed bacilli. Subsequently, inconstant results were reported by Franchetti (28) although upon intravenous injection some of his toxins produced diarrhea, prostration, posterior paralysis, and in some cases coma and death. Toxic filtrates from cultures of this organism were also obtained by Zwick and Weichel (29) and acute symptoms of intoxication were produced in

laboratory animals upon administration. From these experimental results it might seem that the toxic substance produced by *Bacillus paratyphosus* B was of the nature of an endotoxin, but Ecker (30), has shown that both exotoxin and endotoxin are produced by this organism. Ecker also noted that the toxic filtrates were fairly heat-resistant as they retained their toxicity after boiling at 100°C. for five minutes. More recently Geiger, Davis and Benson (16) have conducted a series of experiments with various members of this group of bacteria, in which filterable toxic substances were sought for, and confirmed, in general, the observations of earlier workers. Briefly, it was found that *Bacillus paratyphosus* B produced toxic substances twice as frequently as *Bacillus paratyphosus* A that there was great variability among their strains in the production of toxic bodies, and that apparently the elaboration of such bodies by *Bacillus enteritidis* was even more variable than in the case of the human paratyphoids. Furthermore, these poisonous filterable substances were sometimes thermostable to the extent of resisting boiling at 100°C. for ten minutes. These observations on *Bacillus enteritidis* do not stand alone however, as Gaertner (31) had previously demonstrated the heat-resistant character of the toxins produced by this organism and van Ermengem had confirmed these findings in another series of tests. From these results it appears that this organism produces both an endo- and exo-toxin of comparatively low potency but of some thermostability.

SYMPTOMS AND ILLUSTRATIVE OUTBREAKS

The clinical picture in various epidemics of paratyphoid-*enteritidis* food poisoning is practically the same in all instances, although there may be more or less variation in the details in individual cases.

After the consumption of the infected food, there is always a short incubation period before the onset of any symptoms. Savage, analysing a series of 112 British outbreaks, observed this period to vary from one-half to forty hours or more, while

Geiger has stated that symptoms are usually manifest in two to four hours, and Rosenau says onset may be in four hours or less, or that it may be delayed seventy-two hours or more. In different outbreaks the time of onset undoubtedly varies and there may be considerable variation in different cases, even in the same epidemic, but an average, based on the experiences of many observers, seems to be between six and twelve hours. This variation in the elapsed time before the appearance of symptoms is readily accounted for if the possibility that such poisoning may be of the nature of either an infection or intoxication is admitted, or a combination of both, and therefore, dependent upon the number of organisms taken in or the amount of preformed toxin consumed with the food.

In the great majority of cases the onset is sudden and the general picture is that of severe gastro-intestinal irritation, not infrequently accompanied by symptoms indicative of involvement of the nervous system. Onset is frequently preceded by a chill and headache, shortly followed by severe abdominal pains that may be griping. Pain in other parts of the body, as in the back or limbs, is not uncommon. Accompanying the abdominal distress, nausea, vomiting, and diarrhea are usually observed. The diarrhea is generally severe, consisting of frequent and offensive bowel discharges. As the attack progresses, the stools tend to become watery, and frequently have a greenish cast. Prostration, which is severe and protracted, is often noted. In some cases, there may be collapse. A rise in temperature to 102°F., or 103°F., is generally observed, and there may be nerve involvement as indicated by the restlessness, muscular twitchings and drowsiness of the patient. In some cases, numbness and cramps, herpes, erythematous or urticarial rashes followed by desquamation, have been seen, but these are comparatively rare.

The severity of the symptoms is variable, all degrees, from fulminating cases resulting fatally, within twenty-four to thirty-six hours, to those exhibiting only slight malaise and diarrhea, being reported. Probably the severity of the attack

is dependent upon such factors as the virulence of the particular strain of organism involved, the length of time and temperature at which it has grown in the food, the number of organisms ingested and the susceptibility of the individual eating the food. Usually the attack is over in one to three days, followed by prompt and uncomplicated recovery, but occasionally the patient is ill for several weeks and there is marked and persistent prostration.

Illustrative outbreaks. Outbreak I. Savage (32) has reported a typical outbreak in Murrow, England, due to the use of meat from a diseased animal. The pork bones implicated in this outbreak were bought from a local butcher and used to make brawn. About twelve hours after being made, the brawn was emptied out of the dish, and the same dish, without being washed, was again used in the preparation of some asparagus and potatoes. Four persons partook of these vegetables at the noon meal and all of them exhibited the usual symptoms of food poisoning within twelve to eighteen hours.

Two days later the brawn was given away and was eaten by fourteen persons, all of whom exhibited similar symptoms in eighteen to forty-eight hours after its ingestion. No one partaking of the brawn escaped, and three of the eighteen persons involved in the epidemic died.

At the time of the investigation none of the brawn could be obtained for examination but from the only fatal case examined a paratyphoid group organism was recovered. Further evidence as to its connection with the outbreak was obtained by the demonstration of specific agglutinins for this organism, in high dilutions of the serum from three other patients.

In this outbreak, it is obvious that some ingredient used in the preparation of the brawn was infected with an organism that survived the temperature at which the brawn was prepared, and subsequently infected the vegetables served from the same dish. Inquiry elicited the information that the bones used in making the brawn had come from a pig suffering from an infection of one leg, no doubt due to the organism recovered from the fatal case, in this instance *Bacillus aertrycke*.

Outbreak 2. Perry and Tidy (33) have reported an epidemic in which it was shown that a pathogenic organism, derived almost certainly from a chronic human carrier, was ingested with the food and subsequently became established in the intestines of those who ate it. An unusual feature in this outbreak was the appearance of secondary cases due to contact, in a community in which there were many acute carriers. This method of spread seldom takes place except under such conditions as existed in the present case, namely the aggregation of a large number of individuals in a very restricted community, as in a military camp.

In this epidemic 1060 men reported an attack of diarrhea and were isolated for clinical and bacteriological investigation. This number probably does not represent the total number that suffered from diarrhea in various degrees, and exhibited other symptoms of food poisoning. The period during which the epidemic lasted was about twenty-four days. In individual cases there was a latent period before the appearance of symptoms, after which, onset was sudden and characterized by severe abdominal pain and diarrhea, vomiting very generally, chills, sweats and headache frequently, and in some cases, syncope. In the mild cases, there was no elevation of temperature while in the severe forms slight pyrexia of 99°F. to 99.5°F. was frequent and in some cases the temperature reached 100°F. to 101°F. for a day or two. Usually the tongue was clear but occasionally there was slight fur. The stools were soft and watery, seldom containing blood and with no mucous. The pulse was rapid in the acute stage, the heart sounds were normal, the spleen was not palpable and no rash was observed. Pneumonia and albuminuria were not reported. Prostration was severe but recovery of strength rapid. After the attack the bowels were irregular, and following the mild cases, constipation was often persistent. Diarrhea was frequently noticed after a severe attack.

In this epidemic thirty-five men were subsequently isolated as potential sources of infection after the initial attack, as they continually discharged the organisms in their stools.

Contrasted with the usual experience in food poisoning outbreaks in which a feature is the simultaneous appearance of symptoms in a number of people, who have eaten some particular food in common, it is to be noted, that here, the cases occurred over a comparatively long time. This observation served to direct attention to the possibility that a carrier was involved, and examination of the kitchen personnel disclosed the fact that one of the cooks had suffered from a persistent diarrhea. When the stools of this person were examined it was found that he was excreting *Bacillus aertrycke* and might very well have been the source from which infection of the food came.

Outbreak 3. A third type of outbreak of food poisoning has been reported by Salthe and Krumwiede (34). In this instance the paratyphoid organism involved was of rodent origin and the infection spread through the medium of crumb cakes and eclairs, the filling for which became contaminated from the droppings of mice in the bake shop. Forty-nine persons who ate the food were affected, the appearance of symptoms varying from one to forty-eight hours after consumption of the pastry, and the illness was characterized by nausea, vomiting, cramps, diarrhea, some fever, headache, and prostration. There were no fatalities.

Examination of successive samples of feces, blood and urine, from the employees in the bake shop was negative but after some investigation suspicion fastened on the cream filling of the eclairs, cream puffs, and cream-filled crumb cakes. When investigated it was found that a paratyphoid organism which was identified as *Bacillus pestis caviae* was present in this filler, and the same organism was recovered from the stools of a number of individuals involved in the epidemic. Further inquiry demonstrated the fact that rodent carriers of this organism were present in the shop, as examination of mice feces found on the shelves disclosed the fact that *Bacillus pestis caviae* was present in some of the droppings.

In these epidemics, particularly those reported by Savage

and Salthe and Krumwiede, all the features commonly met with in food poisoning outbreaks are seen. In each instance there is a typical set of symptoms, a number of cases widely separated, geographically, but connected by ingestion of a common food, and finally a specific organism shown to be the etiological agent. Furthermore, they serve to illustrate the various ways in which food may become infected.

PATHOLOGY

From the severity of the gastro-intestinal symptoms it might be anticipated that definite pathological changes in the stomach and intestine would be found, but actually the alterations are comparatively slight. Congestion and swelling of the mucous membranes of the stomach and intestines, together with petechial hemorrhages are usually observed. The Peyer's patches are unaffected and there is no ulceration. The kidneys show cloudy swelling and the liver and spleen are congested but the heart is normal.

Other pathological appearances are not usually observed.

DIAGNOSIS

There are only two really important diseases from which a differential diagnosis has to be made, namely, dysentery, and enteric fever, and on clinical observation alone the distinction can hardly be drawn. In the case of dysentery or ulcerative colitis, some information may be obtained from the character of the stools, as usually there is only a small amount of blood in the discharges from food poisoning cases, and then only during the acute stage, while there is complete absence of mucus, even when the diarrhea is persistent. From enteric fever, food poisoning differs in the rapidity of onset and attainment of its maximum severity.

Definite diagnosis cannot be made, however, except on the basis of laboratory findings, in which the specific infecting organism is isolated from the suspected food, or from the blood,

urine, feces, or viscera of the patient. In this connection it should be borne in mind that, as a rule, the organisms disappear from the patient's stools within two weeks after the appearance of symptoms, so it may be necessary for the pathologist to have recourse to agglutination tests in order to identify the causative organism. In these tests serum from the patient is used against various organisms of the paratyphoid group and that species with which agglutination takes place, is considered the infecting organism.

BACTERIOLOGICAL EXAMINATION OF SUSPECTED MATERIAL

The exact procedure to be followed will vary somewhat with the kind of material to be examined, but in any case, care should be exercised to get a representative sample of whatever substance is to be investigated.

Savage recommends that an emulsion of the material be streaked over a series of lactose-salicin-saccharose neutral-red bile salt agar plates and that another portion be added to tubes of malachite green broth—for enrichment—from which another series of carbohydrate agar plates may be inoculated later. This procedure is favored as promoting the development of the paratyphoid organisms while the growth of the other intestinal organisms is inhibited at the same time. At any rate all white colonies appearing on these plates should be subcultured and a preliminary sorting out of strains affected by means of microscopic agglutination tests, using powerful paratyphoid sera at about one-tenth titre. By this method it is possible to rule out all cultures showing no reaction, and to select those strains that should be studied in detail. Final identification, of course, rests on determination of cultural characteristics and microscopic agglutinin absorption tests.

Other investigators employ a somewhat different technique. For example, Perry and Tidy advocate making the emulsion of the suspected material in peptone broth and inoculating this into tubes containing brilliant green in a dilution of 1-200,000. The action of this dye is to inhibit the development

of many intestinal contaminants and allow the development of a greater proportion of paratyphoid organisms. Following the preliminary enrichment for about twelve hours, plating-out, using Conradi-Drigalski medium, is recommended and any suspicious colonies appearing are identified by the methods above mentioned.

TREATMENT

The treatment, in an attack of food poisoning due to an organism of the paratyphoid group, must necessarily be symptomatic and will depend somewhat on the age and strength of the individual.

The first procedure should be to make certain of the elimination of any material that might be injurious, by emesis or lavage, purging and diuresis. If the symptoms first became manifest shortly after a meal and it is thought likely that the poisonous material may be reached by an emetic, a teaspoonful of mustard in half a glass of warm water may be given. At any rate, vomiting is to be encouraged and gastric lavage with warm saline will be found helpful. Purging, brought about by the administration of an ounce of castor oil or by two grains of calomel followed by a saline will help to eliminate the offending material.

In case there are abdominal pains, hot applications, turpentine stypes or flaxseed poultices may be used. If the pain is severe, hypodermic injections of one-sixth to one-fourth grain of morphine may be resorted to.

Nothing in the nature of food should be given but cracked ice, sips of whey, barley, oatmeal, or albumin water may be allowed.

In those cases exhibiting persistent diarrhea, fifteen grains of bismuth subcarbonate in mucilage of acacia may be given every two or three hours. If diarrhea continues, a mild astringent with or without small doses of codein should be resorted to. In no case should any solid food be permitted until all signs of gastric irritability have subsided.

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CHAPTER III

TUBERCULOSIS FROM MILK AND MEAT

Introduction. Susceptibility of man to tubercle bacilli of bovine origin. Tubercle bacilli in the milk of cows with tuberculous udders. Tubercle bacilli in the milk of cows with no udder involvement but with tuberculosis in other parts of the body. Tubercle bacilli in general market milk. Tubercle bacilli in pasteurized milk. Human infection from the use of flesh and organs of tuberculous animals. Prophylaxis.

INTRODUCTION

Among the diseases of animals that are transmissible to man none has received more attention than tuberculosis. As a result, a vast amount of literature pertaining to the subject, in one or another of its phases, has accumulated, and it is only with great difficulty that one is able to come to definite conclusions in regard to some of the controversial points involved.

In the present discussion we will limit ourselves to a consideration of those aspects of the question directly connected with the transmission of the disease to man through the consumption of meat and milk contaminated with the tubercle bacillus. Accordingly, the questions to be answered are in reality the following:

1. What evidence is there to show that tubercle bacilli of bovine origin can infect man?
2. What evidence is there to indicate that tubercle bacilli are present in the milk of cows with tuberculous udders?
3. What evidence is there to show that tubercle bacilli are present in the milk of cows with no manifest lesions in their udders but with tuberculous lesions in other parts of their bodies?
4. What proportion of the general supply of market milk is infected with tubercle bacilli?

5. What evidence is there that pasteurized milk is a source of infection with tubercle bacilli?

6. What evidence is there to indicate that the flesh or organs of tuberculous animals are a source of infection for man?

Evidence bearing on these various points will be presented in the sections that follow in the hope that the reader may be able to form for himself a reasoned judgment as to each.

SUSCEPTIBILITY OF MAN TO TUBERCLE BACILLI OF BOVINE ORIGIN

For centuries phthisis was described in medical literature but the definition of tuberculosis, as a clinical entity, was delayed until the observations of Laennec. Even then it was believed that the condition in man was probably identical with that seen in animals. That is, there were those who believed that the same agent was involved in the production of the characteristic reaction in both man and animals, and although the nature of this agent was unknown, it was thought that the disease might be transmitted to man from the lower animals, and from one of these to another, through such media as infected flesh or milk. Villemin (1) demonstrated as early as 1865 that the infectious agent in tuberculosis was transmissible by inoculation as the disease was produced in experimental animals when they were injected with tuberculous tissue. Chauveau in 1868, Gerlach in 1869 and Klebs (2) in 1871 succeeded in producing the disease experimentally by feeding the milk from tuberculous cows to animals, and Virchow (3) reviewing the question somewhat later, expressed the view that man might contract tuberculosis from bovine sources through the use of infected milk, particularly if the udder of the cow was affected.

Up to this time the nature of the etiological agent in tuberculosis was unknown but Koch (4) in 1882 announced the discovery of *Bacillus tuberculosis* and after extensive study of the disease in man and in animals, declared; "Bovine tuberculosis is identical with human tuberculosis, and therefore, a disease

transmissible to man." For some years after this the identity of the tubercle bacilli infecting man and animals was generally accepted and it was not until 1898 that Smith (5) conclusively established the fact that there were varieties of the organism characteristic of bovine and of human origin although two years previously—1896—he had intimated that such was the case. It thus becomes a matter of considerably more than academic interest to determine whether the bovine type of bacillus is infectious for man.

Obviously no direct experimental evidence concerning the infectivity of the bovine tubercle bacillus for man is available, but there is very suggestive evidence to be found in experiments in the transmission of bovine tuberculosis to monkeys, in the frequency of primary intestinal tuberculosis in children, and finally in the many cases of accidental infection in man that have been reported.

Ravenel (6) in 1901 presented the first experimental evidence indicating that the bovine type of organism does infect man and in concluding his address before the British Congress on Tuberculosis said, "The bovine tubercle bacillus has a high degree of pathogenic power for man." This conclusion coupled with Koch's (7) assertion that as the result of further investigation he had reversed his earlier position and no longer believed that bovine tuberculosis was transmissible to humans precipitated a controversy that has led to a vast amount of work along this line upon which our present ideas on this subject are based.

Reviewing the literature on this subject Kober (8) reports that cases of the transmission of bovine tuberculosis to man have been recorded by Hamilton (9), Ravenel (10), Troje (11), and many others, and tabulates himself 86 cases of human infection with bovine tuberculosis from milk. More recently Moore (12) has summarized the evidence along this line and cites the conclusions of the British and German Commissions, as well as the independent observations of Park and Krumwiede in New York. The findings of the British Commission showed

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that in England 24 of 108 cases, or 22 per cent of the cases studied, were infected with the bovine type of bacillus, while in Germany 6 of 56 cultures derived from human cases, or 10 per cent, were of the bovine type. In New York, Park and Krumwiede (13) determined the type of bacilli present in 478 cases and cite 1033 other cases from the literature in which the type of infecting organism was determined, and found that in the age groups 0 to 5 and 5 to 16 years there were 5 per cent and 3 per cent infection with the bovine bacillus respectively. Eastwood and Griffith (14) found bovine tubercle bacilli in 55 of 261 cases of bone and joint tuberculosis, and that all but 3 of these were in patients under 16 years of age. Mitchell (15) found the bovine organism in 71 of 80 cases of tuberculosis of the mesenteric glands, while Wang (16) determined infection with the bovine bacillus in 11 of 20 cases that he studied in children under 16 years of age. A review of the literature indicated that infection with the bovine type of bacillus was responsible for 70.3 per cent of the infection in Edinburgh, 21.3 per cent in England and 24.5 per cent in other countries, in children 5 to 16 years of age.

Still another line of evidence, that may be drawn upon to show the susceptibility of man to infection with the bovine type of organism, is found in the numerous cases of accidental infection that have been reported. For the most part these have occurred among veterinarians who have become infected in the course of post-mortem examinations of tuberculous carcasses. Thus Pfeiffer (17) and Tscherning (18) have cited the cases of men who became infected through accidental wounds while examining tubercular cows at autopsy, and Naughton (19) reported the case of a man employed in a slaughter house who became infected through a wound caused by a meat hook. Ravenel (20) reported the cases of two veterinarians infected during the autopsy of tuberculous animals and also observed the interesting case of his laboratory assistant who contracted the disease during autopsy of a goat that had succumbed to an experimental inoculation with bovine tubercle bacilli.

Such instances as the above indicate beyond a doubt that man is susceptible to infections by the bovine type of tubercle bacillus and with this fact established it is of interest to gain some notion as to the presence of these organisms in food materials from which human infection may occur.

THE OCCURRENCE OF TUBERCLE BACILLI IN THE MILK OF COWS WITH TUBERCULOUS UDDERS

To attempt an exhaustive review of the literature on this question is hardly necessary in this place but a few references will serve to indicate the basis upon which our present conception rests. Thus Bang (21) produced tuberculosis in 3 rabbits and 5 pigs by feeding them milk from cows having tuberculous udders and also infected 4 rabbits by the inoculation of similar material. Peuch (22) produced tuberculosis in 4 rabbits by the injections of milk, while De Man (23) was successful in producing the disease in 8 guinea-pigs by the inoculation of milk from tuberculous udders. Subsequently, Russell (24), Rabinowitsch and Kempner (25) and MacFadyean and Woodhead (26) were all able to produce tuberculosis in experimental animals by injecting milk from cows with tuberculous lesions in the udder.

In addition to these instances of experimental tuberculosis produced by feeding or injecting the milk from cattle with tuberculous udders, there are many reported cases in the literature of children presumably infected through the ingestion of infected milk. The implication of the milk supply in such cases rests upon circumstantial evidence, it is true, but Bollinger (27), Uffelmann (28), Law (29), Ernst (30) and Kober (8) among others, have reported numerous cases in which they were reasonably certain the infection was derived from this source.

From this brief resumé of the matter it becomes clear that the milk from cows showing obvious tuberculous involvement of the udder contains tubercle bacilli in sufficient numbers to be infective. It now remains to review the evidence indicating

the infectivity of milk from cattle with tuberculosis in other parts of the body but not suffering from involvement of the mammary gland.

THE OCCURRENCE OF TUBERCLE BACILLI IN THE MILK FROM
COWS WITH TUBERCULOSIS BUT NO UDDER
INVOLVEMENT

Ernst (30) examined microscopically smear preparations of milk from cows with tuberculosis but no infection of the udder and found that 31.5 per cent of the specimens contained tubercle bacilli. MacFadyean and Woodhead (26) obtained 16 per cent infections by inoculating such milk. Bang (31) found that 2 of 21 cows showing tuberculosis without udder involvement, were secreting virulent tubercle bacilli in their milk, while Schroeder (32) infected guinea-pigs with milk from one of 12 cows diagnosed as tuberculous on clinical grounds. Rabinowitsch (33) in examining the milk from 5 dairies where the cattle were subject to frequent veterinary inspection, and therefore might be assumed to be free from infection—found virulent tubercle bacilli in 3 of the 5 cases. Ravenel (34) experimentally infected 10 out of 63 guinea-pigs with milk from tuberculous cows which had no lesions in the udder, and Gehrman and Evans (35) demonstrated that 16 of 41 tuberculous cows with sound udders were excreting virulent tubercle bacilli. Mohler (36) also showed that the milk of 12 out of 56 cows diagnosed as tuberculous, but with no udder lesions, contained tubercle bacilli.

Still another line of evidence may be drawn upon, to show the danger that may lurk in milk which comes from tuberculous animals, even though they have no udder involvement. Here reference is made to those investigations which have shown that these animals may infect the milk in other ways than in the milk ducts. For example, Schroeder and Cotton (37) found that the feces of tuberculous animals frequently contained large numbers of virulent bacilli, and that pollution of the milk with such material was the most common source

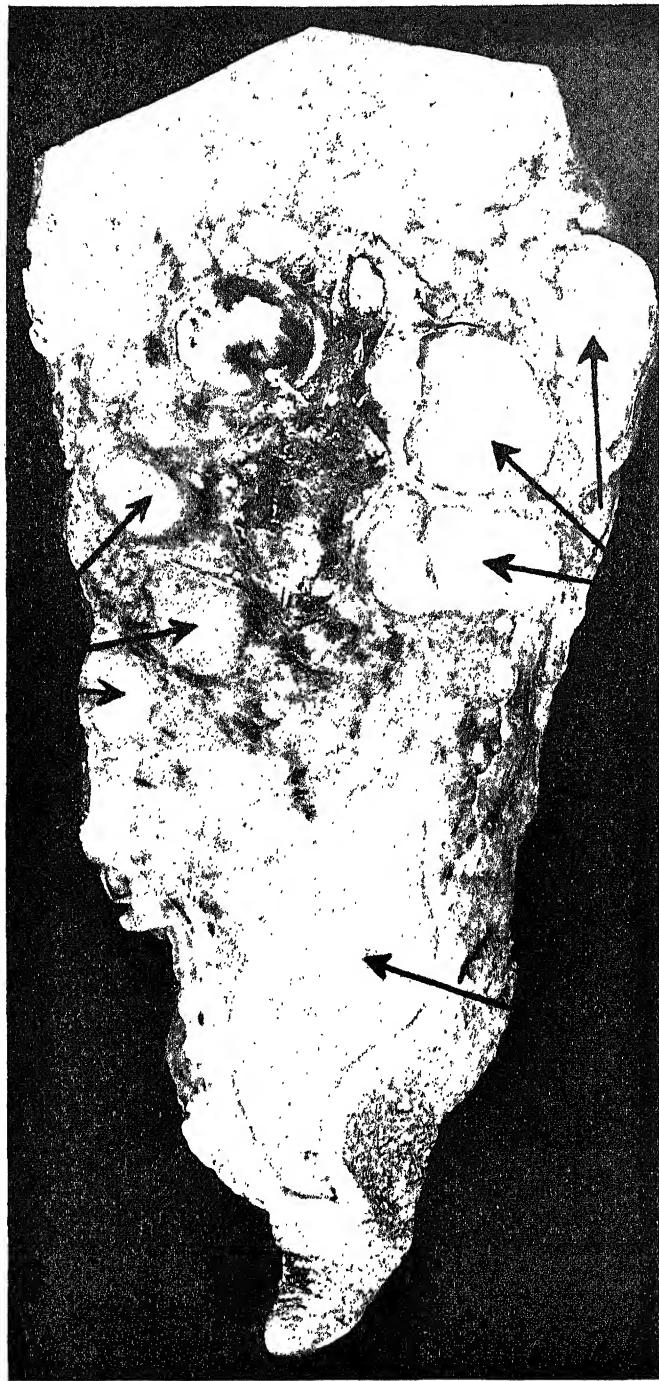


FIG. 1. SECTION OF A TUBERCULOUS UDDER SHOWING WELL-DEVELOPED
LESIONS

Iowa, 13.8. More recently Moak (40) has expressed the belief that 25 per cent of all milch cows are tuberculous, and reports that in New York 641 of 1459 tested were found to react. This is a percentage of 43.9. In another survey Russell (41) reported that 374 reactors were found among 1213 animals tested in one locality, and 127 among 1478 in another. Together the average of these tests indicated that approximately 19 per cent of the cattle tested were tuberculous, and this may be regarded as representing fairly closely the extent of the infection among cattle in general.

From these figures it appears that a considerable proportion of the cattle from which the general milk supply is derived are infected with tuberculosis, but it may be argued that the infectivity of such milk will be reduced to a negligible factor through dilution when it is mixed with uninfected supplies. This is conceivable, but actual examination of samples, taken at random from various city supplies reveals an interesting situation. Rabinowitsch and Kempner (25) found that 28 per cent of the samples examined in Berlin contained tubercle bacilli and MacFadyean (42) at the Jenner Institute found 22 per cent of the samples he examined were contaminated with these organisms. In New York City Hess (43) found 16 per cent of the samples infected; Anderson (38) in Washington, obtained 6.7 per cent positive results from the samples examined and Bartlett (44) found that 44 per cent of the samples taken from the mixing vats in New Haven contained virulent tubercle bacilli.

Such results as these indicate the potentially dangerous nature of general market milk and emphasize the necessity for the strictest control of this food by the public health authorities. This means that every effort should be employed to make this product safe for human consumption but chiefly through regulation of the pasteurizing process as laxity in the performance of pasteurization may lead to the development of a sense of false security in the public mind.

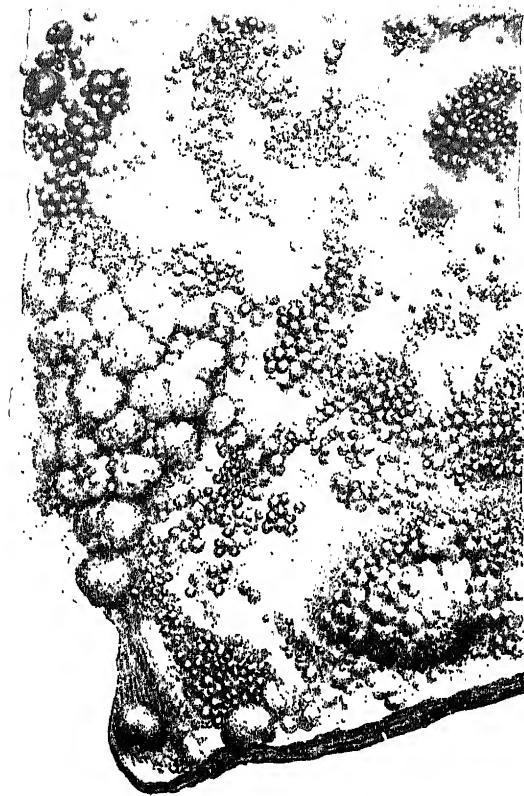
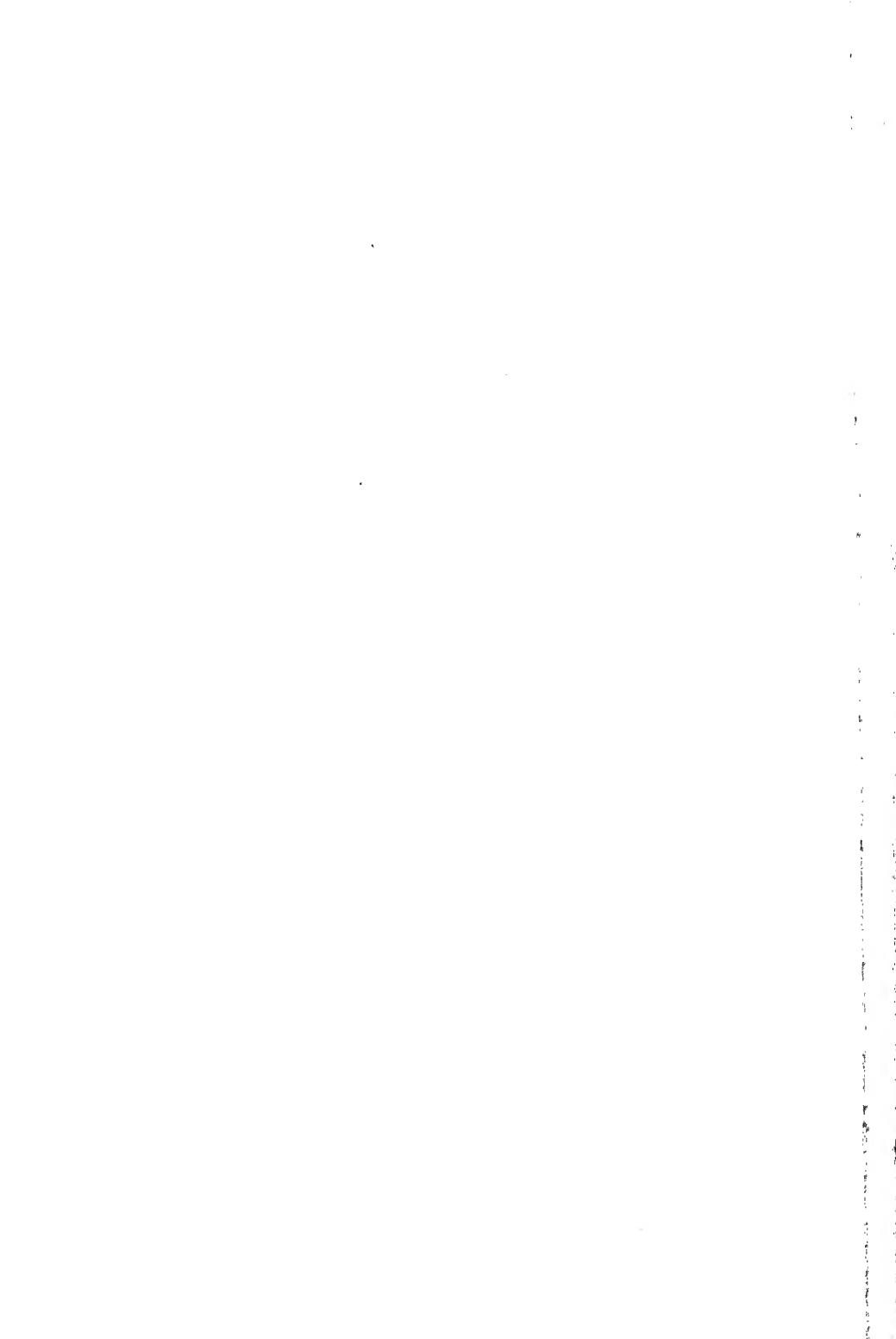


FIG. 2. SMALL NODULAR TUBERCLES FROM THE PLEURA OF A COW



THE OCCURRENCE OF TUBERCLE BACILLI IN PASTEURIZED
MILK

Numerous instances have been cited above to show that tuberculous cows, with no clinical signs of the disease, may excrete virulent tubercle bacilli in their milk, and it has also been shown that a considerable portion of the general market milk contains these organisms. Not all of these organisms necessarily come from tuberculous cattle, it is true, but whatever the source the fact remains that such infected milk is a menace to the consuming public. This forces us to the conclusion that the only real safeguard against possible infection lies in such treatment of the supply as will render it non-infectious, that is, in pasteurization. This process, if properly carried out, offers absolute protection to the public but unless thoroughly controlled cannot be relied upon. As indicating this fact it is to be noted that Hess (43) demonstrated virulent tubercle bacilli in 1 of 8 samples of pasteurized milk and Campbell (45) showed that 1 of 12 samples of similarly treated milk contained viable organisms.

HUMAN INFECTION FROM THE USE OF FLESH AND ORGANS OF
TUBERCULOUS ANIMALS

The sources from which human infection may occur, aside from milk, are the flesh and organs of such animals as are subject to infection with the bovine bacillus, as the avian and piscine organisms are not usually pathogenic for man. Among the food animals that are susceptible to the bovine type of tubercle bacillus we know that cattle, pigs and sheep are frequently infected, while goats are seldom, and rabbits rarely subject to the disease. The infection of horses is known to occur, but the use of this meat as food is not common enough to warrant much consideration. From this it becomes clear that the real sources of danger for man are the infected flesh and viscera of such animals as are generally used for food namely, cattle and hogs.

In the case of these species it is to be borne in mind that not only the muscle but all parts of the body may be potentially infectious, as the various organs, such as the liver, lungs, mesentery, udder and intestines are utilized in one way or another as food. This being the case it becomes obvious that the danger of human infection from such material is more real than imaginary, as the most common sites of infection in cattle are in the bronchial and mediastinal glands, lungs, pleura, peritoneum, mesenteric glands, liver, udder and kidneys, while lesions in the muscular tissue are comparatively rare. In pigs the infection tends to be more generalized, but the intestines, lungs, mesenteric glands, and bones are very often involved while lesions in the flesh are rare, as in cattle.

Generally speaking, the muscle of tuberculous animals is not dangerous except in the case of local extension of lesions into the muscular tissue or when the bacilli are in the circulating blood. Such local extensions occur relatively infrequently but may happen in the acute stage of the disease, when foci of infection have become softened and purulent, or a tuberculous lesion has encroached upon and caused ulceration of the intima of a blood vessel or the thoracic duct, thus bringing about a discharge of organisms into the circulating blood. When any of these events occur the flesh or muscle juice of such animals becomes infectious for other animals as shown by experimental evidence in which feeding or inoculating healthy animals with such material has led to the development of the disease. By inference the same possibility of infection exists for man as well.

Littlejohn (46) summarizing the matter of infection from tuberculous flesh, cites the experiments of Nocard who infected 1 of 4 guinea-pigs by inoculation with the muscle juice of a cow with generalized tuberculosis. Galtier also infected rabbits by inoculating similar material and Gerlach infected pigs by feeding the flesh of a tuberculous sheep.

From such results as these it appears that the flesh of tuberculous animals may at times contain virulent tubercle bacilli

but this source of infection is of comparatively little importance and the real source of danger to man lies in the consumption of glands, lungs, livers, udders, and intestines of tuberculous animals in which a large amount of infectious material may be ingested with a small amount of tissue.

PROPHYLAXIS

From a review of the literature, to which brief reference has been made above, it appears to be conclusively demonstrated that man is susceptible to the bovine type of tubercle bacillus and that this organism is responsible for a considerable amount of infection in man, particularly in that part of the human population which uses large quantities of milk in its diet. It also appears that tuberculous cattle with or without udder lesions may contribute more or less contamination with virulent tubercle bacilli, to the general milk supply and that the flesh or organs of such animals are a potential source of human infection.

In view of these facts it becomes obvious that the sanitary control of milk and meat should be most rigorously enforced. All meat should be carefully inspected before offered for sale and all milk should be properly pasteurized if the public is to be adequately protected from the possibility of infection from these sources.

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CHAPTER IV

UNDULANT FEVER FROM MILK

Historical. Etiology. Symptomatology. Pathology. Diagnosis. Differential diagnosis. Treatment. Prophylaxis.

HISTORICAL

Malta fever has been known for many years as endemic in the Island of Malta. It has also had a variety of other names, such as Mediterranean, goat, or Gibraltar fever, among numerous others, but the designation of Undulant Fever seems to be the most logical, as it indicates one of the outstanding features of the infection, namely, the peculiar remittent type of fever.

The disease has existed for centuries in the countries along the Mediterranean, although it was not recognized as an entity until the classical studies of Marston, when it was differentiated from typhus and typhoid fever and was designated by him as Mediterranean Remittent Fever. Since that time, it has been recognized as a cosmopolitan disease and is now known to exist not only in Spain, France, Italy, Greece, Northern Africa, the Levant, and India, but in Ceylon, East and Southern Africa, China and Russia, and in North and South America as well. In fact, it has been established by Lake (1) that the disease has occurred in epidemic form in Arizona, and it is said by Tappan (2) to exist endemically in the goat-raising sections of New Mexico, Arizona, and Texas, and in Mexico, along the Rio Grande river.

The causative organism was isolated by Bruce (3) in 1886 from spleen cultures of human cases of Malta fever made at autopsy. With it he produced the disease in monkeys. Subsequently, the disease was studied most comprehensively by the British Commission for the Investigation of Mediter-

ranean Fever and most of our current ideas in regard to it are based on this work.

ETIOLOGY

The micrococcus which Bruce (4) showed to be the etiological agent of the disease and to which he gave the name *Micrococcus melitensis* is extremely pleomorphic and exists at times in a coccobacillary form. It is an extremely minute aerobic, non-sporulating, Gram negative organism, is non-motile, does not liquefy gelatin, and grows slowly on the glycerin, serum, or blood agar plates used in its isolation. Frequently, there will be no sign of growth on such plates within four days after they are inoculated. The isolation of the organism is best accomplished by hemoculture, although it may also be recovered from the urine, milk, spleen, liver, kidneys, lymphatics, and sometimes, from the feces of infected animals.

In the more recent literature of this subject a great deal of confusion as to the nomenclature and exact generic relationship of the micrococcus discovered by Bruce, is to be found. This has been especially pronounced since the recognition of the close relationship existing between the *melitensis* and the *abortus* group of organisms. A very helpful study of this matter has been made by Meyer and Shaw (5) who proposed the generic name *Brucella* for the whole group of organisms and this has met with general acceptance. In this case the abbreviation becomes *Br.*, to avoid confusion with the abbreviation for the genus *Bacillus* and the different groups become *Brucella abortus* and *Brucella melitensis*, in this way indicating their bovine or caprine source.

The natural source of infection for man is through the use of goats' milk or its products, as the goat is the natural host of the organism, although it has been shown that pigs, ewes, asses, horses, mules, cows and monkeys, are susceptible to the infection. In goats the organism frequently is found in the blood of apparently healthy animals and in such cases the milk of the animal contains agglutinins for the organism. Such

infected goats suffer no inconvenience from their infection and there are no lesions in their udders.

In the case of human infection it is probably true that in the majority of cases it is derived from the goat and occurs through the intestinal canal, but there are recorded instances in which the infection has taken place via other routes and from other sources. Magnani and Morandi (6) have reported definitely tracing the infection to the use of sheep's milk, while Tyndale and Viko (7) have reported a fatal case in which the infection took place through a wound on the hand, into which the organisms penetrated during the process of handling the infected placenta from a goat.

Brucella melitensis is a resistant organism and is viable even after 80 days' existence in dust and after a month in water. This is of considerable significance in the spread of the disease under natural conditions and it is thought that the spread of infection among goats is principally through contaminated food or drinking water. Other modes of infection are through the respiratory and cutaneous systems, but these are of relatively slight importance. In those areas in which the disease is endemic the percentage of infected animals is considerable, as surveys have shown that 34.0 per cent of the goats examined in Algeria harbor the organism, 29 per cent in St. Marthal, 30.7 per cent in Tunis, 34.2 per cent in Marseilles, and 50 per cent in Malta; while Lake (1) found 18.3 per cent infected in Arizona and 19.4 per cent infected among the animals examined in Texas.

SYMPTOMATOLOGY

The incubation period of Undulant Fever varies from six to fourteen days and the onset of the disease is characterized by chills, malaise, headache, anorexia, insomnia, depression, and muscular pains. Neuritis, especially involving the peripheral nerves, is often observed, and a sudden and acute attack of sciatica may afford the first clue as to the nature of the illness. The circumflex and perineal nerves are less frequently

involved than the sciatic. The temperature rises in step-like progressions from day to day for about five days, attaining a higher point on successive evenings and falling a trifle each morning. By the fifth day it has generally reached 104°F. to 105°F. with a pulse of 80 to 90 and the headaches and muscular pains are more severe. The tongue is slightly coated, but the tip and edges are red and the throat more or less congested. At the same time the voice may be husky, there is often a slight cough, and there are signs of a slight bronchitis. The spleen may be tender and often is palpable; and there is constipation in the majority of cases, although sometimes there is a slight diarrhea.

These symptoms continue without any marked change for about fourteen days, when the temperature begins to fall, and the other symptoms ameliorate, during a period of about two weeks, when there is a relapse and the pyrexial period is repeated. During each relapse the initial symptoms are considerably lessened in severity and in the intervals of apyrexia the patient is much better, although naturally weakened by each attack.

This undulating course of the disease continues usually for three to four months, but cases have been observed in which it persisted as long as three years. If the case becomes chronic there is anemia, which shows a great reduction in the red cells, but an even more marked fall in the hemoglobin percentage and a moderate leukopenia in which the polymorphonuclears show a greater reduction than the lymphocytes. At the same time there is gastric irritation, painful spleen, cardiac disturbance, and not infrequently sponginess and bleeding of the gums. In some cases lobar pneumonia develops. Usually the patient is dejected and nervous almost to the point of hysteria, while insomnia is frequent and each febrile attack is accompanied by profuse sweating. With each recurrence the condition of the patient becomes worse and eventually desquamation of the skin, abscesses and ulcers in the ilium, sometimes hemorrhages even, and increasingly more painful and

swollen joints, with pains in the sacroiliac region, orchitis, and inflammation of the parotid glands may be observed.

These symptoms may be regarded as characteristic of more or less typical cases and generally abate in the course of three or four months. But there are three other types of the infection which are not infrequently seen, and which deserve some consideration. Of these the *malignant* type is one in which the onset is sudden and the temperature rises to 104°F. or higher very rapidly and is accompanied by severe headache, acute and generalized pains in the muscles, vomiting, diarrhea, congestion of the lungs, and at times pneumonia. In a few days the condition simulates typhoid fever. Death takes place from cardiac failure in one to three weeks after the onset of the disease. A second unusual type of case is known as *intermittent* and is usually mild in its course. Onset is characterized by slight chilliness, malaise, nervous irritability, night sweats, and a low fever. This condition persists for several weeks or may even last for six months, and the patient is unaware of the serious nature of his illness until he is debilitated and weak. Finally, there is the *ambulatory* type of case in which there is an almost complete absence of symptoms except for occasional feverishness and sensation of weakness. In these cases the organism can usually be recovered from the blood stream and the patient is really acting as a carrier of the disease.

PATHOLOGY

The pathological processes due to infection with *Brucella melitensis* have not been studied to any great extent, due to the comparatively small number of fatal infections. It is recognized that the organism gets into the blood stream from the alimentary canal by penetrating the intestinal wall and produces a true septicemia, which is accompanied by a characteristic swelling, softening, and congestion of the spleen. Hemolysins, agglutinins, and specific immune bodies, result from the infection, and it has been shown that the agglutinins, at least, persist for a long time. It has been maintained by

some students that one attack of the disease confers a lasting immunity, although Eyre (8) and other workers have suffered second attacks.

In those cases that have come to autopsy, the spleen is enlarged, softened and congested in all cases, while in the majority of instances there is more or less congestion in the liver, kidneys, mesenteric glands, duodenum, jejunum, and large intestine. The spleen is generally dark red in color and friable in texture, and the Malpighian bodies exhibit some swelling. The liver is enlarged and congested and on section shows cloudy swelling with round-cell infiltration between the lobules. The kidneys are congested and in some cases there is evidence of glomerular nephritis, while in the intestinal canal there is congestion and in certain cases there may be ulceration following hemorrhages. In the lungs there is more or less marked congestion and there may be patches of consolidation.

DIAGNOSIS

The outstanding features of the disease are the peculiar undulating course of the fever, the enlarged spleen, the heavy night sweats, the marked involvement of the joints with swelling and severe pain but no redness, and, as the infection becomes chronic, the development of marked debility and secondary anemia.

Positive diagnosis of the condition can only be made by laboratory tests, and of these hemoculture, agglutination with serum from which group agglutinins have been removed, and complement fixation are of the most assistance. To be considered of value the agglutination test must be positive in dilutions of the serum of 1:80 or higher, and it has been suggested by Nicolle and Conor (9) that false reactions may be obviated by separating the serum from the clot if it is not to be used at once. On the other hand, Nègre and Reynaud (10) rule out false reactions by heating the serum to be tested, at 56°C. for 30 minutes in this way destroying the non-specific agglutinins and leaving the specific antibodies free to act in the presence of their own particular antigen.

In culturing the organisms from the blood, urine, or material obtained from splenic puncture, it is best to inoculate the material first into a relatively large amount of slightly alkaline nutrient broth for enrichment purposes. The usual practice is to withdraw about 5 cc. of blood into sodium citrate solution, at the height of the fever curve preferably and, if possible, late in the day, and then discharge this into about 45 cc. of nutrient broth. After 3 to 10 days' incubation at 37°C., transfers from the enrichment culture are made to agar slants and these examined for growth 4 to 7 days later. If growth takes place the organism is then identified by cultural and serological methods.

DIFFERENTIAL DIAGNOSIS

Those diseases with which Undulant Fever may be confused are typhoid fever, malaria, and kala-azar. Unlike malaria, the majority of cases do not have a sudden onset and there is an absence of severe rigors. There is also an absence of plasmodial parasites in the blood and any large increase in mononuclear cells, while there is usually an increase of lymphocytes. At the same time, treatment, with quinine has no effect on the course of the disease. From kala-azar, Undulant Fever differs in that the spleen is not so noticeably enlarged and is soft, while an examination of material obtained by splenic puncture will reveal the presence of leishmaniae in the former disease. Differentiation from typhoid fever is assured by agglutination tests, in which the patient's serum is used against a known culture of the typhoid bacillus and by inability to culture the typhoid organism from either the blood or feces.

TREATMENT

In the mild cases there is little need of drugs, but if the case be acute the patient should be kept in bed and given a light, but not necessarily fluid, diet. Daily sponge baths with warm water are helpful, and when the fever is high cold sponges and ice packs are indicated. The patient should be assured of a

regular evacuation through the administration of moderate doses of compound licorice powder or an enema every other day. No drug has been found that has a specific action against the infecting organism. For alleviation of the severe headache small doses of aspirin together with a little caffeine may be used, and if there are joint pains they will be relieved by these drugs at the same time, although morphine compounds may have to be used in addition. To overcome the sleeplessness, bromides or paraldehyde will usually suffice, although morphine is indicated if the insomnia is due to pain. To relieve the persistent vomiting that is sometimes observed, a little cooled soda water or two drops of tincture of iodine in an ounce of cinnamon water may be tried.

Treatment of some cases with vaccines made from *Brucella melitensis* alone, or consisting of combinations of *Brucella melitensis* with other organisms, such as *Bacillus typhosus* or the paratyphoid organisms have been recommended by Castellani (11) and has been of some use in chronic cases, although in acute cases such therapy is contraindicated. More recently Khaled (12) has reported remarkable improvement in three cases as the result of injections of a vaccine made from *Brucella abortus*, an organism closely related to *Brucella melitensis*, and Nicolle, Burnet, and Conseil (13) have shown that live abortus organisms may be given to healthy individuals with impunity and have suggested their use in the prophylaxis and vaccine therapy of undulant fever.

PROPHYLAXIS

Complete abstinence from the use of raw goats' milk or the products made from it, such as butter and cheese, is the surest way to avoid infection. However, if the milk must be used, it may be rendered harmless by boiling.

In the matter of excreta from an infected person, as the organism is present in both urine and feces, these should be thoroughly disinfected before they are disposed of.

The real control of this disease rests upon the elimination

of infected animals. For this reason it has been recommended that all goats used for milk purposes be tested periodically for infection in much the same fashion as is done with dairy cattle for tuberculosis. In conducting such tests the diluted milk is first used as a source of agglutinins for a known strain of the organism and if a positive or suspicious reaction is obtained, the blood serum of the animal in question is then used in a confirmatory test. By this process a herd of milch goats can undoubtedly be maintained free from infection.

Khaled (12) has succeeded in immunizing both monkeys and goats by intravenous injection of killed suspensions of the closely related organism, *Brucella abortus* and in this way rendered these animals insusceptible to subsequent inoculations with virulent cultures of *Brucella melitensis*. Further employment of this practice may demonstrate that this is a procedure that is capable of use on a large scale in the protection of goats from infection with the organism of undulant fever.

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CHAPTER V

SEPTIC SORE THROAT FROM MILK

Historical introduction. Symptomatology of septic sore throat. Etiology. Bacteriological diagnosis. Management of an epidemic.

INTRODUCTION

In general, the production of sore throat, or tonsillitis, due to infection with streptococci, has only a remote connection with the consumption of food. From time to time, though, a peculiar type of sore throat, occurring in epidemic form, and almost invariably connected with an infected milk supply, has been reported. This epidemic type of sore throat has come to be known as septic sore throat, and is well differentiated from ordinary sore throat or tonsillitis. The differentiation rests on a more or less characteristic clinical picture, the explosive nature and extensiveness of the outbreaks, and the epidemiological and laboratory evidence that shows the etiological relation of the disease to the use of infected milk.

Outbreaks of this nature have long been recognized in Great Britain and the milk supply has been implicated in almost every instance, but recognition of the disease in the United States was delayed until only a few years ago. In fact, the first investigation of such an epidemic was made by Winslow (1) in 1912, when an extensive outbreak occurred in Boston, in which 1400 individuals were involved. Since that time, outbreaks of 1,000 cases in Baltimore; 10,000 cases in Chicago; 1,000 cases in Concord, New Hampshire; 669 cases in Cortland and Homer, New York; 348 cases in Jacksonville, Illinois; 325 cases in Galesville, Wisconsin; and 487 cases in Portland, Oregon, have been reported and investigated. This is not an inclusive list by any means, but it serves to illustrate the extensiveness of some epidemics and their widespread geographical distribution.

SYMPTOMATOLOGY

Onset, in epidemic tonsillitis, is usually sudden with chilliness, fever, sweating, headache, muscular pains, and loss of appetite. The throat is congested, the tonsils are swollen and there may be soreness on swallowing, while there is frequently a yellowish exudate that covers the pharynx which has somewhat the appearance of a membrane. In contrast to a true diphtheritic membrane, when removed, the underlying tissues show by no means as much laceration as in diphtheria. Generally, the submaxillary lymphatic glands are somewhat enlarged and tender. At the same time there is an elevation of temperature to 101°F. or 103°F. which subsides in three to five days, leaving the patient weak and exhausted.

When recovery is uncomplicated, it is usually rapid and complete, but if the infection is followed by complications, it may be extremely protracted. The complications observed are diverse and are due to extension of the infection or to absorption of the toxin produced by the infecting organism. If the bacteria enter the blood stream there is frequently metastatic involvement of distant organs.

Direct extension of the infection via the Eustachian tubes leads to otitis media, and when penetration is deeper, to mastoiditis. If metastases occur the organisms seem to exhibit a preference for the heart muscle and valves, or for the joints, resulting in endocarditis or rheumatic arthritis. More rarely neuritis, keratitis, or nephritis has been observed and in a few instances numerous cases of adenitis and peritonitis have been reported during the epidemic.

ETIOLOGY

Septic sore throat seems beyond doubt due to infection with hemolytic streptococci. In part, the evidence implicating these organisms rests upon epidemiological grounds, and in part upon laboratory examination of material taken from the throats of patients, as well as infected milk as delivered to the consumer or drawn from the udder of the cow.

In regard to the identity of the streptococci involved in causing epidemic tonsillitis Savage (2), Smith and Brown (3) and others, showed that a variety of these organisms could be obtained from the throats of patients in these outbreaks. It was also found that the streptococci involved were not necessarily identical in different epidemics, either in the same or different localities.

In the course of these investigations the question of the relation of mastitis in the cows and the appearance of septic sore throat among the consumers of the milk was studied. The result was, expressed in their opinion, that the streptococci commonly associated with the production of bovine mastitis or garget are of no significance in the production of septic sore throat in man. These mastitis streptococci were also shown by the workers mentioned above, and by Davis (4) to possess little or no virulence for laboratory animals although in the course of the investigations strains of hemolytic streptococci were isolated from diseased udders, that did possess some virulence for experimental animals. These strains resembled the type of hemolytic streptococcus obtained from human sources, rather than those from gargety cows.

Having observed that there seemed to be types of hemolytic streptococci that were more or less constantly present in mastitis and septic sore throat, Savage (2) performed upon himself the crucial experiment of inoculating his own throat with *Streptococcus mastitidis*. In this way he hoped to determine whether the hemolytic streptococcus, most commonly met with in gargety milk, had any pathogenicity for man. Fortunately, the culture proved to be entirely innocuous.

In his next experiments Savage (2) reversed the condition of the above test and sought to show that hemolytic streptococci of human origin might cause bovine mastitis. In this he was not successful. But finding that occasionally hemolytic streptococci, having the characteristics of the human type, were found in the udders of cows with mastitis, he was led to hypothesize an explanation as to the origin of epidemic tonsil-

litis. As he put it, "the cow in this class of infection is only potentially pathogenic for man when it acts as an active or passive carrier of organisms of *human* origin."

From these observations and similar results obtained by numerous other workers, among whom may be mentioned Smith and Brown (3), Davis (4), and Mathers (5), we have presumptive evidence that the bovine hemolytic streptococci occurring in milk are not responsible for the production of disease in man. On the other hand, it appears that streptococci from cases of human sore throat are capable of gaining a foothold in the udder of the cow and in this way may infect the milk supply. Such organisms may thus cause epidemic tonsillitis among consumers of the milk.

In the literature, there are numerous examples of epidemics in which the above chain of events has in all probability led to outbreaks of septic sore throat. In Portland, Oregon, Benson and Sears (6) isolated identical streptococci from the throat of a worker in a dairy, from one quarter of the udder of a cow in the herd and from the throat of a patient suffering from epidemic sore throat. In this instance the probability seems to be that the dairyman infected the udder of the cow and this in turn infected the general milk supply, when the milk from all the cows was pooled. Thus the infection was carried to a large number of consumers who subsequently developed the disease. Almost the same train of events was encountered in the Rockville, New York, epidemic that was investigated by Krumwiede and Valentine (7). By far the great majority of cases occurred among the customers of a single dairy and bacteriological investigation showed that hemolytic streptococci were present in the udder of one of the cows in this herd, and that they were identical culturally and immunologically with strains obtained from the throats of patients suffering from epidemic tonsillitis. Examination of the employees failed to show any individual suffering from sore throat and the cow involved showed no signs of mastitis. In view of these findings Krumwiede and Valentine stress their

belief, that in tracing such epidemics particular efforts should be made to locate cases of sore throat among the milk handlers and that the investigation should not be limited to examination of the cattle alone. It thus appears that these writers support the view originally advanced by Savage, and independently expressed by Smith and Brown, namely, that the cow is significant in the etiology of septic sore throat, only as she acts as a carrier of hemolytic streptococci of human origin.

BACTERIOLOGICAL DIAGNOSIS

The correct diagnosis of a particular case, as being one of septic sore throat, rests upon the more or less characteristic clinical features, combined with the epidemiological data obtained in the investigation of other similar cases appearing at about the same time, and supported by the laboratory identification of cultures of streptococci from the throats of patients, from the milk supply, from the udder of one or more cows in the herd from which the supply is derived, and if possible from the throat of a person who comes in intimate contact with the milk in the course of its preparation for delivery.

It must be said, however, that there is not complete agreement among bacteriologists as to just what features characterize the streptococci that are of pathological significance in septic sore throat. Thus Bundesen (8) tentatively recommends that only those organisms should be regarded with suspicion which possess the proper streptococcus morphology, that produce colonies of the beta-hemolytic type on blood agar, that elaborate hemolysins sufficient to cause full hemolysis of rabbit corpuscles in two hours and that kill both of two mice injected, acutely, within forty-eight hours. When cultures having these characteristics are isolated from milk, such milk may be regarded with suspicion, but these data are only to be regarded as suggestive and not as proof that the cultures would be at all harmful to human beings.

Subsequent to this definition of the type of organism that would be regarded with suspicion in Chicago, Brown, Frost,

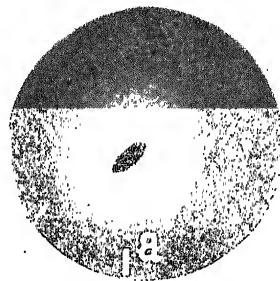
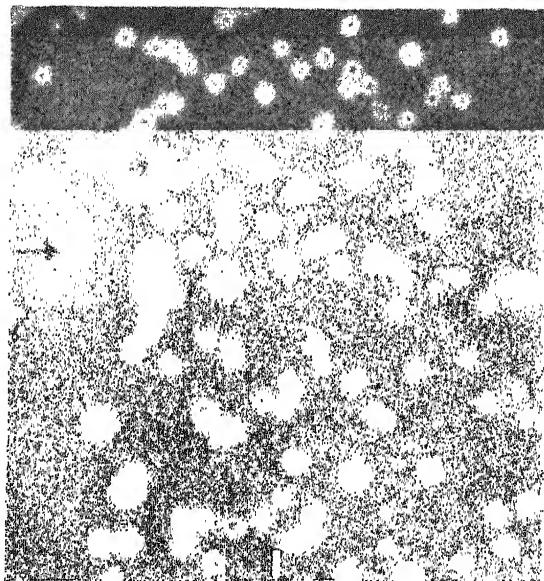


FIG. 3. (1) COLONIES OF BETA HEMOLYTIC STREPTOCOCCI ON BLOOD AGAR.
(1a) PHOTOMICROGRAPH OF DEEP COLONY INDICATED BY ARROW IN
FIGURE ABOVE. AFTER BROWN



and Shaw (9) made an intensive study of the matter and established certain new standards that they believe should be conformed to by any strains of streptococci that may be considered questionable from the standpoint of the possible production of septic sore throat in man. Naturally, these investigators stressed the adoption of any tests that would help to differentiate the streptococci of human and bovine sources, and, in this connection, finally settled on the following tests as of the greatest differential value; (a) the recognition of the type of colony produced on blood agar plates, as defined by Smith and Brown (3) and Brown (10); (b) the hemolytic titer in fluid media, as determined by Brown (11); (c) the final hydrogen ion concentration attained in glucose broth cultures, as measured by Ayers (12), Ayers, Johnson, and Davis (13), and Avery and Cullen (14); (d) and finally, the hydrolysis of sodium hippurate, as determined by Ayers and Rupp (15).

As a result of this investigation, in which a large series of cultures derived from certified milk, septic sore throat, and from sporadic human infections were studied, they conclude that the ordinary beta-hemolytic streptococci found in milk, whether from gargety or normal cows, are of no significance to man and that the causative agent in milk-borne septic sore throat is *Streptococcus epidemicus*. This organism is probably of human origin, but may infect the udder of the cow, and in this way gain entrance into the milk supply. Culturally and biologically it is different from the hemolytic streptococci commonly present in milk, and may be differentiated from them and identified by the application of the tests mentioned above.

As a routine procedure for the detection of *Streptococcus epidemicus*, Brown, Frost, and Shaw, recommend the following technique:

- (1) Milk should be inoculated into poured blood agar plates.
- (2) Capsules should be looked for in moist india ink preparations from young moist surface colonies.
- (3) Deep colonies with beta zones of hemolysis are to be fished into serum broth. To save time, fishings from the same colonies may be made into glucose broth and into sodium hippurate broth.

(4) From the broth culture make:

- a. A hemolysin test, adding 0.5 cc. of a 5 per cent suspension of washed rabbit blood corpuscles to 0.5 cc. of broth culture.
Take care not to contaminate the broth culture so that it may be used for subsequent tests. Cultures producing little or no hemolysis in two hours at 37°C. may be discarded and subsequent tests omitted.
- b. A stock culture on a blood agar slant. Capsules should again be looked for after incubation overnight.
- c. Inoculate sodium hippurate broth if it has not already been inoculated directly from the colony. By means of the ferric chloride test, hydrolysis of sodium hippurate may be detected in 24 or 48 hours.
- d. Inoculate glucose broth, if it has not already been inoculated directly from the colony. The final hydrogen-ion concentration should be determined in not less than 48 hours.
- e. Inoculate salicin and mannite broths. Saccharose, lactose, and raffinose have seldom been found of value for this differentiation.
- f. Mice may be inoculated, although the pathogenicity test has been found less significant than the others.

To justify condemnation of the milk the streptococcus found should correspond in all respects to *Streptococcus epidemicus* as this is the species most often encountered in septic sore throat. In Table I the characteristics of *Streptococcus epidemicus* are given, together with those of a typical bovine streptococcus, from certified milk, and for contrast the reactions of a typical streptococcus—*Streptococcus pyogenes*—from sporadic cases of sore throat are included. From this brief summary of the biological characteristics of the beta-hemolytic streptococci it appears that the cultures derived from epidemic tonsillitis, and known as *Streptococcus epidemicus*, form a quite homogenous group that may be readily distinguished from the typically bovine type of beta hemolytic streptococcus or those found in sporadic cases of sore throat.

MANAGEMENT OF AN EPIDEMIC

Obviously, in an epidemic of septic sore throat, the nature of the outbreak necessitates getting at the source of the infection as rapidly as possible, and also makes the application of isolation and quarantine measures useless. For this reason, it

TABLE I
Differential features of beta hemolytic streptococci from septic sore throat, bovine sources and sporadic cases of tonsillitis
 (Compiled from the data of Brown, Frost and Shaw)

TYPE OF THE CULTURE	CAPSULE	HEMOLYTIC CAPSULE	PATHOGENETIC FOR MICE	FERMENTATION REACTIONS				FINAL pH IN DETRUSOR BREATH AFTER 48 HOURS	SOURCE OF STRAIN
				Lactose	Sucrose	Mannite	Galactose		
<i>S. epidemicus</i>	+	4+	Usually fatal within 48 hours	+	+	+	+	0	Septic throat demic
Certified milk.....	0	Variable	Usually not fatal [¶]	+*	+†	Vari- able	Vari- able	5.5§	Bovine
<i>S. pyogenes</i>	0	4+	Usually fatal within 48 hours [¶]	+	+	0	+	5.0§	Sporadic hu- man cases of sore throat

* One strain that did not attack lactose was encountered.

† One strain that did not attack sucrose was encountered.

‡ Occasional strains do not hydrolyze sodium hippurate.

§ In the final pH there is some overlapping but roughly the limits given will hold.

¶ These are the usual results obtained when 0.5 cc. of culture is injected intraperitoneally.

is essential that the field investigation commence at once with a canvass of the houses in the affected area. In this way a record of the supply of milk, cream, ice cream, or other dairy products will be obtained, along with the number of persons ill and their symptoms, and this information, together with that obtained from hospitals and institutions, will undoubtedly direct attention toward one or more possible sources of infection. At the same time cultures taken from the throats of typical cases may serve to provide a lead for further investigation. At any rate, if suspicion is in any way directed toward the dairy, it should be inspected and attention given to the apparatus and methods of handling the milk. An examination of the throats of all dairy employees should also be made, and any individuals exhibiting sore throats should be at once excluded from further handling of the milk until their throats clear up.

More important than the examination of the dairy employees is the study of the individual cows on the farms from which the milk supply comes. In this way only can the source be determined from which the streptococci are coming and the milk from the cow or cows affected be kept out of the general supply.

In the meantime insistence on thorough pasteurization of the milk supply, if it has really been the source of the epidemic, will have checked its spread at once and the further investigation may be more or less protracted without prejudice to the public health.

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CHAPTER VI

ACTINOMYCOSIS

Introduction. Etiology. Symptomatology. Pathology. Diagnosis. Treatment.

INTRODUCTION

This disease occurs not only in man, but among the lower animals as well, among which cattle, horses, sheep, and swine are particularly affected. In cattle, it passes by the name of "lumpy jaw" or "wooden tongue," and in many human and animal cases the etiological agent is the same species of actinomycetes, although there are other species of the fungus that are known to possess pathogenic properties. The exact method by which the infecting agent gains entrance into the human body is by no means certain, but inasmuch as the actinomycetes are widely distributed in the environment, it is presumed that infection takes place very frequently as the result of chewing objects, such as grain, pieces of straw, grass, or splinters of wood.

Actinomycosis is essentially a chronic infectious disease characterized by the formation of indolent granulomatous tumors, which tend to break down, discharging a seropurulent fluid, in which the peculiar sulphur-yellow granules composed of aggregations of the fungus are seen. In the literature of this subject, acute cases have been recorded, and the appearance of the disease in this form should be borne in mind, although in most instances it tends to run a chronic course. This is indicated by the fact that in pulmonary infections it has sometimes been referred to as non-tuberculous phthisis or pseudotuberculosis. Further confusion has been introduced by authors who have reported instances of this infection under the names of streptothrix, cladothrix, or nocardia infections.

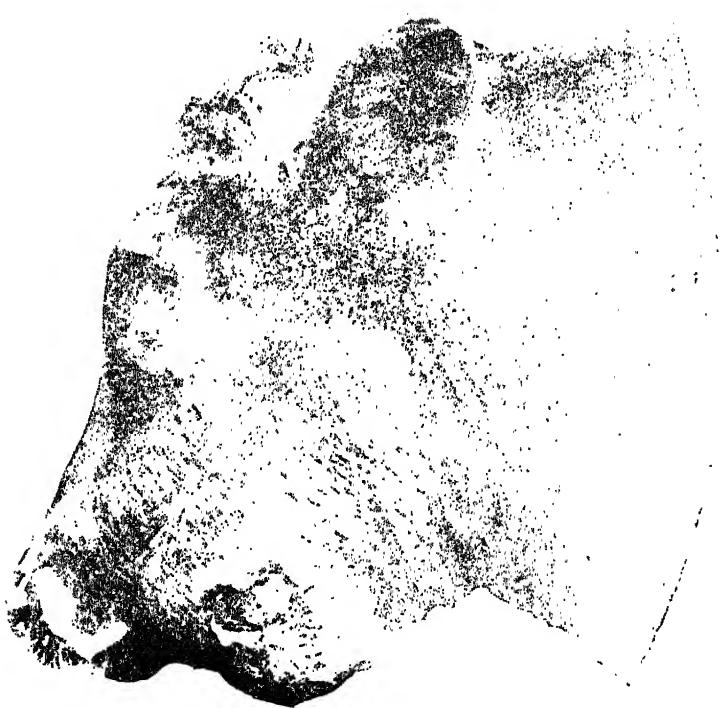
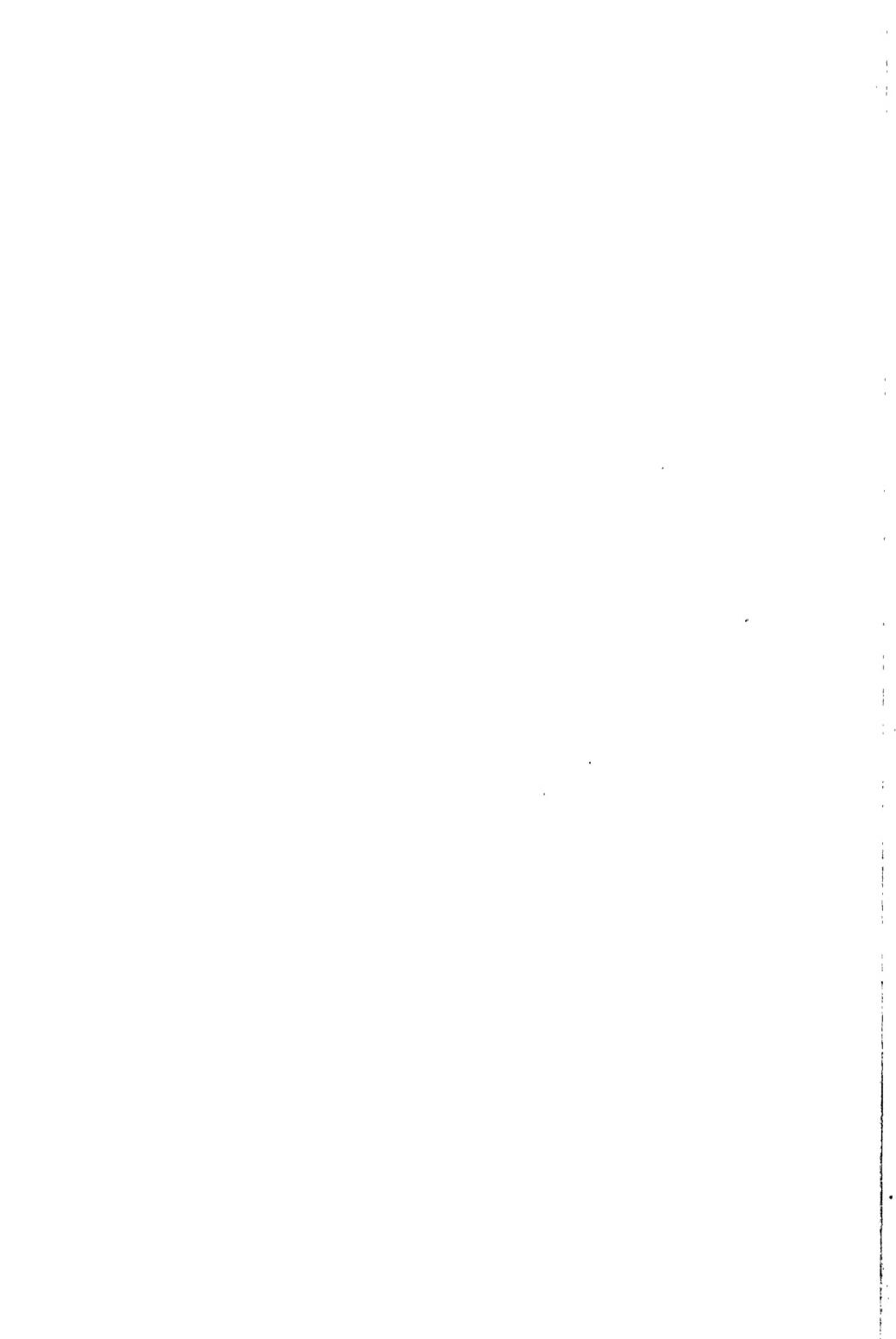


FIG. 4. LUMPY-JAW OR ACTINOMYCOSIS, IN A COW. AFTER MOORE



The basis for such distinctions rests upon insecure foundations apparently, and in this discussion it is proposed to consider all infections caused by organisms of this group as actinomycosis.

No structure of the body is immune from infection with actinomycetes, as is indicated by the fact that the infection occurs in the cervico-facial region in about 50 to 55 per cent of the cases, and of the remainder about 20 to 25 per cent involve the organs of the abdominal cavity, 13 per cent the organs of the thoracic cavity, 3 per cent the tongue, and the remainder appear in the skin.

ETIOLOGY

The so-called ray fungus was first described by Harz (1) from a bovine case of lumpy jaw, and was shown by him to occur in the form of a central network of interwoven threads, with radiating bulbous mycelia, from which appearance the popular name was derived. It is an anaerobic organism, is Gram positive and, in some strains at least, is acid-fast. It was called *Actinomyces bovis* by Harz. Similar organisms have been isolated from actinomycotic lesions by Wolff and Israel (2), Wright (3), Harbitz and Grondahl (4), and a number of other investigators. On the other hand, aerobic filamentous organisms have been reported by Boström (5), Foulerton (6), Berestnew (7) and others as being the etiological agents in cases of actinomycosis. From a critical review of this matter it would seem that there are both aerobic and anaerobic species of the fungus that are capable of producing clinical actinomycosis.

SYMPTOMATOLOGY

The incubation period in these infections generally extends over a period of months, and after the disease becomes apparent, its course is usually slow. Often the first evidence of the infection is seen in the presence of a hard, lumpy swelling about which the skin is indurated and reddened. This area later becomes softened and breaks down, with the discharge

of a seropurulent fluid in which many very small yellowish granules are seen. These bodies are made up of masses of the fungus. About the sinus openings of the lesion granulomatous tissue soon begins to form.

From the primary lesion the spread of the infection is by continuity of tissue without regard to anatomical boundaries, according to Kellock (8), and adhesions are frequent, due to the penetration of all structures with which the fungus comes in contact. At times, however, it appears to be carried by the blood to organs far removed from the original site of infection, and under such conditions metastatic processes are observed. Such a case was reported by Martin (9) in which the primary lesion was in the lungs, but in which a metastatic actinomycotic lesion in the brain occurred. In such cases, and in many others in which the lesion is obscure, the symptoms are very difficult to interpret and the diagnosis is often incorrectly made.

The most characteristic cases are those in which the primary lesion occurs on the face or in the thorax. In these cases the path of infection is very frequently via the parotid gland, through carious teeth, or by direct inhalation of dust particles bearing the organisms. In some instances the infecting organism has gained entrance through the agency of a foreign body that becomes lodged in the tissues. In these cases the disease usually spreads to include the lungs and for a period in its course it is frequently mistaken for tuberculosis.

PATHOLOGY

Histologically, the lesions of actinomycosis are those of infectious granulomata in which the fungus is observed embedded in a central amorphous granular mass surrounded by a zone of plasma cells. About this there appears an area of lymphoid elements among which a few giant and mast cells may also be seen.

DIAGNOSIS

The absolute recognition of the condition rests upon finding the etiological agent in the purulent exudate from the lesion.

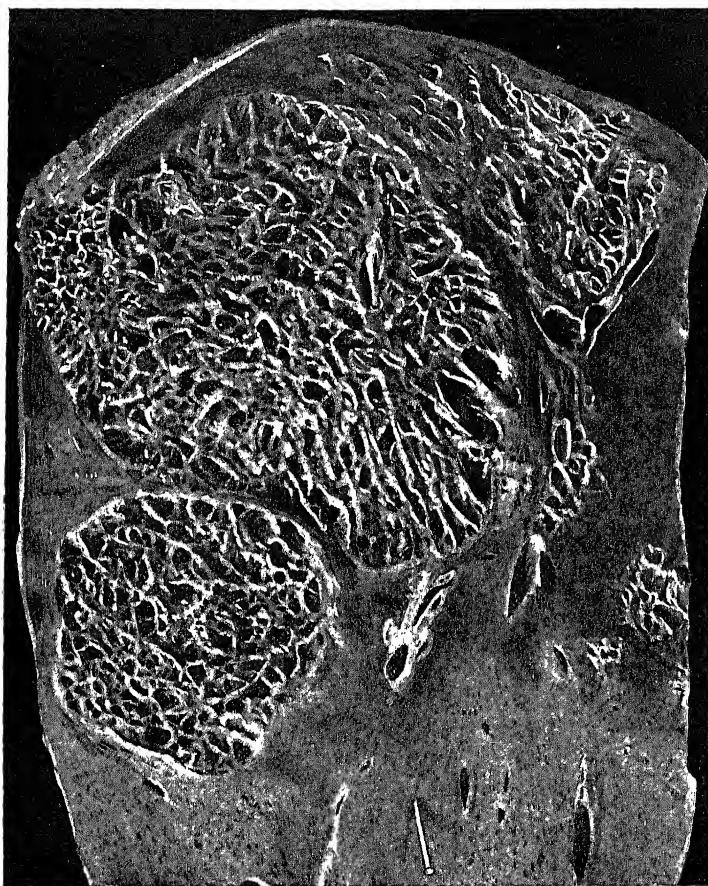


FIG. 5. SECTION OF LIVER FROM A CASE OF ACTINOMYCOSIS IN MAN. AFTER
McFARLAND



This may be accomplished by microscopic demonstration of the ray fungus in the sulphur-yellow granules in the exudate, or by its cultivation from the granules. In the examination of the granules they are usually crushed between glass slides and examined or smeared out on the slide in the usual way and stained by Gram's method before being examined. If cultivation is to be attempted, the granules are washed in several changes of sterile water and then macerated in the depths of a tube of melted dextrose agar. In this way the organisms are distributed throughout the medium, and if it is an anaerobic species, colonies will develop which may be later transplanted to other media for further identification. This is the technique of Wright (3). At the same time, however, surface inoculations should be made on the surface of agar slants or in bouillon in order to observe the growth of any aerobic species that may be present.

In the routine examination of sputum for tuberculosis, it frequently happens that no tubercle bacilli can be demonstrated in samples derived from patients presenting many of the signs of pulmonary tuberculosis, even though the examinations are frequently repeated over a considerable period of time. In such cases, the possibility of infection with actinomyces should be borne in mind and the sputum scrutinized very carefully for the presence of Gram-positive thread, rod, or spore forms. In this connection the observations of Claypole (10) are of some importance as indicating what to look for in the sputum. This investigator has reported that the expectoration is quite characteristic and may be of two types: (1) glairy, mucilaginous, often quite watery; (2) purulent, more or less bloody, and with a foul odor, sometimes intensely fetid. In either case there is variation in its amount, while the second type may have a characteristic, homogeneous, pinkish color, or may be deeply blood-stained.

From such sputum the minute sulphur-yellow granules may be picked out, washed free of debris and mounted on a slide for examination. Under low magnification the color of the

granule is accentuated, the center is usually relatively light, but becomes darker and may even be brown at the edge, while under higher magnification it will be seen that the center is made up of a mass of interwoven threads, which radiate toward the periphery. When stained, these threads exhibit a more or less banded appearance and seem somewhat granular.

TREATMENT

The treatment of actinomycotic infections usually consists of local surgical measures, supplemented by the administration of potassium iodide in large doses, and in some cases the subcutaneous injection of a vaccine.

In connection with the use of potassium iodide, the observations of Wild (11) are of considerable interest, as he has observed that small doses do not always prevent the spread of disease and in one case improvement was not seen until the patient was given 240 grains of the drug daily. Under such treatment the possibility of iodism naturally comes to mind, but this only occurs when the doses are too small to exert a diuretic effect. In any case, it will probably be found necessary to continue the treatment over a period of several months.

The use of vaccines in the treatment of actinomycosis has had only a limited trial and the results have not been altogether satisfactory, but in some instances encouraging results have been observed. Thus we find that Malcolm (12) and Collie (13) among others have reported complete recovery of patients under vaccine treatment, while Harbitz and Grondahl (4) and Kinnicutt and Mixter (14) have reported instances in which fatal termination of the disease was not prevented by such measures. The latter authors give in detail the method for the preparation of vaccines.

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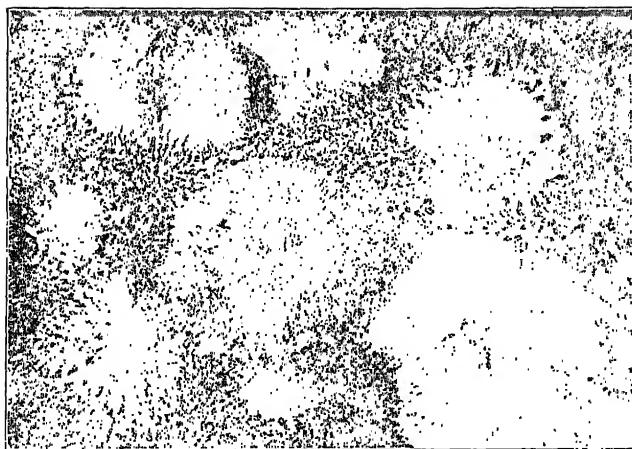


FIG. 6. GRANULE OF ACTINOMYCES CRUSHED BETWEEN GLASS SLIDES, SHOWING RADIAL STRIATIONS. NOT STAINED. AFTER MCFARLAND

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PART II
INTOXICATIONS FROM FOOD

symptoms of botulism in man or in animals. Incidentally, it may be noted that the European strains have produced the disease by the elaboration of their toxin in food stuffs of animal origin almost exclusively, that only two of the American strains have been identified in outbreaks of the disease in man, that the food substances implicated in American outbreaks have been of animal or vegetable origin indiscriminately, and that the Australian strain has produced the disease in domestic animals alone.

SYMPTOMATOLOGY AND DIAGNOSIS

Clinically a great variety of symptoms is observed in cases of botulism, but in general, the cases fall into two quite distinct groups, i.e., those in which there is an initial acute gastro-intestinal disturbance followed by symptoms of intoxication and those in which the typical symptoms of botulism become manifest at once. The nervous symptoms are brought about as the result of absorption of the toxin in the food through the mucosa of the upper intestinal canal, as shown by Bronfenbrenner and Schlesinger (3).

In the United States about one-third of the cases of botulism have exhibited preliminary signs of acute gastro-enteritis, i.e., nausea, vomiting, and diarrhea, which come on about twelve to thirty-six hours after eating the toxic food and which are probably due to local irritation of the alimentary tract by the decomposed food which has been ingested. These features disappear with the onset of typical nervous symptoms. In the remaining two-thirds of the cases there is an immediate action upon certain portions of the peripheral nervous system as shown by Dickson and Shevky (4) and Edmunds and Keiper (5).

In the cases observed in America, Geiger, Dickson and Meyer (6) state that the earliest recorded onset of the disease is two hours, while the most delayed is eight days after the consumption of the toxic food. The matter of elapsed time between the ingestion of the toxic material and the appearance

of the first symptoms is not to be stressed too much, as there is great variation in individual cases.

In those cases presenting primary gastro-intestinal symptoms there is usually an initial feeling of lassitude and fatigue, frequently accompanied by dizziness or headache and a burning sensation with some distress in the region of the stomach. At the same time there may be nausea and vomiting with or without diarrhea. These symptoms are transitory, seldom persisting beyond 48 hours, and when diarrhea is absent there may be an early and persistent constipation which can be regarded as one of the outstanding characteristics of the disease. Not infrequently the intestines are inflated without rigidity, tenderness or pain.

The disturbances of vision which soon follow are often the first indication of the serious nature of the illness and the dimness of vision experienced is seemingly dependent upon the loss of ability to accommodate, as distant objects can be distinctly seen with either eye alone. Very early in the illness the third cranial nerve is usually involved accompanied by blepharoptosis, loss of reflex to light stimulation, mydriasis and diplopia. The pupils are often irregular in contour and unequal, and complete loss of accommodation soon follows. The external rectus muscle is earlier and more frequently impaired functionally than the superior oblique. Photophobia has been observed in a few cases and nystagmus and vertigo are not uncommon. That there is no disturbance of the retina is agreed to by the majority of observers.

Swallowing and talking become difficult coincidentally with or shortly following the appearance of visual disturbances and the patient often complains of a sensation of constriction in the throat. The difficulty in swallowing is largely due to functional impairment of the pharyngeal muscles and efforts to swallow frequently result in strangling spells which may persist until the patient is exhausted. During these attacks regurgitation of fluids through the nose and insufflation into the trachea and bronchi frequently occur. At the same time the

tongue becomes somewhat enlarged, is sluggish in its movements, and is heavily coated on the surface although clear along the edges, the voice is low and loses its tone and finally there is complete aphonia. Even in the mild cases there is a very evident and early fatigue of the muscles of the throat and in talking the articulation becomes noticeably slower and more difficult, and the voice becomes increasingly husky. One of the salient features of botulism is the extreme muscular weakness exhibited by the patients and in those cases where the muscles are completely relaxed, the patient is unable to raise the head, arms, or legs and the condition simulates paralysis, although actually it is very rare to observe true paralysis of the skeletal muscles. In the more mild cases, incoördination of the muscular movements of the arms and legs occurs and progression is often with an ataxic gait, but there is very rarely any impairment of the reflexes of the skeletal muscles.

Sensory disturbances are generally completely absent in botulinus intoxication, although there may be initial headaches and gastric distress; in a few cases there have been numbness and tingling of the extremities, while occasionally there are tinnitus and partial deafness, but as a rule there is an absence of pain.

Mentality is usually unimpaired during the intoxication and often there is great apprehension of impending death. In the early stages of the illness restlessness, insomnia and sometimes hysterical attacks are observed, but as the intoxication progresses, the patient becomes more and more apathetic or even somnolent; he may be extremely irritable when he is aroused, due apparently to his inability to make himself understood and to swallow. In a few cases convulsions have been reported and occasionally coma appears shortly before death, but usually the mind remains clear and the patient is acutely aware of the probability of a fatal issue.

Secretions are often inhibited and there is dryness of the mouth, pharynx and nasal passages, although a few cases are on record in which the flow of saliva has been increased.

Sweating may or may not take place, but if it occurs the sweat has a peculiar offensive odor; otherwise the skin becomes dry and hard. Both oliguria and anuria have been observed, a fact that is not remarkable when one considers the difficulty of swallowing. In none of the cases has there been noted any characteristic change in the urinary constituents.

The body temperature usually varies between 96.0°F. and 98.6°F. and, in uncomplicated cases, remains subnormal during the whole illness; in many cases fever may appear during the last days of the intoxication, due to the development of bronchopneumonia.

As the disease progresses the action of the heart muscle becomes impaired to such an extent that there may be no visible cardiac impulse and the heart sounds are feeble and distant. Coincidently the pulse rate, which has been slow during the early stages of the intoxication, may become rapid and become as high as 130 to 160 per minute. This combination of subnormal temperature and rapid pulse is one of the striking features of the disease.

Blood counts have failed to indicate any typical blood change, although the data at present available do not justify drawing any definite conclusions on this point.

Respiration in the early stages of the disease is not disturbed, but as the intoxication progresses breathing becomes difficult and labored, sometimes of the Cheyne-Stokes type. As the respiratory muscles become fatigued there may be partial or complete asphyxia and death is usually due to cardiac or respiratory failure. Often there is terminal asphyxia with cyanosis, and occasionally the patient dies in a strangling spell.

Recovery, in those cases in which it takes place, is an extremely slow and tedious process. The strangling and difficulty in speaking and swallowing usually improve first, but the muscular weakness and disturbances of vision are slow to abate. In many cases the patients are comparatively well in two or three months, but the weakness, vertigo, emaciation and sometimes disturbances of vision may persist for months.

When convalescence is complete there seems to be no permanent disability.

MORTALITY

In a total of 134 outbreaks involving 458 cases, Geiger (7) reports 309 deaths, or a mortality rate somewhat over 65 per cent. More recent summarization of the statistics of the disease show that to the end of 1926 there have been in the United States, Canada and England 151 outbreaks including 518 cases and 347 deaths. This establishes a fatality rate of about 67 per cent. From these figures it will be seen that the mortality rate is very high, as compared with the rate of other types of food poisoning, although in individual epidemics there may be a wide variation; in some instances it is relatively low while in others it may reach 100 per cent.

The mortality rate in those cases characterized by initial gastro-intestinal symptoms varies but little from that in those exhibiting symptoms of botulism at once. Geiger, Dickson and Meyer (6) report that in a series of 180 individuals affected 71.8 per cent of those showing acute gastro-intestinal symptoms, and 73.2 per cent of those in which there were no such symptoms, terminated fatally.

PATHOLOGY OF BOTULISM

At necropsy the victims of *Bacillus botulinus* intoxication show no characteristic gross lesions and the only constant finding is the decided congestion of the central nervous system and of the abdominal and thoracic organs. Scattered hemorrhages may be present in the brain tissues, which may be edematous, and there may be multiple hemorrhages around the base of the brain and in the upper part of the cord. The lungs are congested and often show areas of bronchopneumonia; the heart muscle is soft and flabby; the liver, kidneys and spleen are hyperemic, and all the parenchymatous organs are opaque and cloudy on section. There may be ecchymoses and hemorrhages on the serous surfaces and in the lungs.

All the tissues show marked congestion and often the arteries, veins and capillaries are engorged with blood. There may be many larger or smaller perivascular hemorrhages around the distended vessels in the brain and meninges, and in the brain and especially in the lungs there are often large hemorrhages extending beyond the vicinity of the vessel.

In patients who have succumbed slowly to the disease, the presence of cellular thrombi in the blood vessels of the brain first described by Wilbur and Ophüls (8) is very suggestive of *Bacillus botulinus* intoxication. But even when found, they cannot be considered as pathognomonic of botulism, as was shown by Dickson (9), when he found similar thrombi in material from a case of death due to pneumonia following mustard gassing, and also in another case of death due to epidemic encephalitis. In none of the victims of botulism which have come to autopsy in the hands of these observers or in the hands of Edmunds (5) has there been any indication of destruction of the ganglion cells, as was described by Marin-esque (10) and Schübel (11). It is emphasized by Edmunds (5) that there are no degenerative lesions and that all the essential symptoms of botulism can be explained by an incomplete curare-like paralysis of the endings of the motor nerves to the voluntary muscles, accompanied by a more or less complete paralysis of the parasympathetic nerve endings.

Some difficulty has been experienced in differentiating between botulism and epidemic encephalitis on the basis of microscopic examination of tissue. The distinction should not be difficult though as perivascular lymphocytic infiltration is one of the characteristic features of epidemic encephalitis and is not seen in botulism.

THE BACTERIOLOGY OF BOTULISM

The discovery by van Ermengem in 1895 of *Bacillus botulinus*, during his investigations of an outbreak of food poisoning, introduced a new conception as to the nature of such cases. Up to that time it had been thought that such

epidemics were always due to the action of one or another member of the group of organisms known as the paratyphoid-enteritidis group. This discovery showed that there was a second and distinct type of case due to the intoxication of the patient from absorption of preformed toxin in his food.

For some eight years after the discovery of *Bacillus botulinus* it was supposed that some product of animal origin was essential for the growth of van Ermengem's bacillus, and it was not until an outbreak in Darmstadt in 1904 was traced to the consumption of beans in which toxin had been elaborated that attention was directed to the possibility that foods of vegetable origin might be involved as well. From this observation the disease was shown to have wider significance than had been imagined, and from that time the efforts of many investigators have been directed toward the discovery of the natural sources of the organism and the study of its biological characteristics. The result of this work is that at the present time there have been described several strains of bacilli in Europe and the United States capable of giving rise to the toxic syndrome characteristic of botulism. Not all these cultures are identical and they fall quite naturally into several groups composed of organisms varying in their cultural characteristics or producing different types of toxin. Because of these dissimilarities, it would seem wise to bring together the available information and point out wherein the various types differ from each other and from the culture described originally by van Ermengem. The comparison of the modern cultures with the original strain is rendered somewhat difficult due to the fact that the van Ermengem strain is now extinct, but there is an English strain known as the Lister No. 94 which more nearly resembles it than any of the American types and with which these may be compared.

The descriptions here given differ in certain respects from those reported in the literature by some investigators who have worked with these organisms, but it may be pointed out that

Reddish (12) has investigated a number of the American strains that have been passing as pure and found them to be contaminated. It should be emphasized that the cultural characters here reported are those obtained by Bengtson (13) using cultures obtained by the single cell method of isolation and shown to produce a toxin giving rise to the characteristic symptom-complex of botulism in experimental animals.

The van Ermengem Strain. The organism described and named *Bacillus botulinus* by van Ermengem was a large anaerobic bacillus with rounded extremities, occurring singly, in pairs, and rarely in chains. The spores were terminal or sub-terminal and somewhat wider than the rod. Motility was slight, and when stained by the method of Gram the organism retained the gentian violet, although in old cultures the decolorizing action of alcohol was very rapid. On glucose gelatin the colonies were round, transparent, yellowish-brown, and granular. Gelatin was liquefied, but there was no attack on other protein media and in media containing glucose gas was formed, although in the presence of lactose or saccharose there was no gas formation. In various media a slightly rancid but not unpleasant odor of butyric acid was produced. The optimum temperature for growth was between 20°C. and 30°C. while 37°C. to 38°C. was unfavorable for growth and toxin production. The spores were destroyed when exposed to 80°C. for 30 minutes, or 85°C. for 15 minutes.

Lister No. 94 Strain. Of the numerous strains now extant, that described as Lister, No. 94, in the publications of the Medical Research Committee of Great Britain, most nearly approaches the characteristics of the van Ermengem culture and with this the American types may be compared.

This organism is an anaerobic bacillus with rounded ends, occurring singly, in pairs and sometimes in chains. The spores are usually terminal and somewhat wider than the rod, although some spores may be central. When detached the spores are oval. In young cultures—7 to 8 hours old—the

organism is Gram-positive, but in older cultures, especially in meat, the Gram fastness is soon lost. In hanging drops the organisms are markedly motile, and in this respect they differ from the van Ermengem culture. Gelatin is liquefied after some delay, but there is no proteolytic action on other media. The organism grows best in media containing glucose and liver infusion. The reaction observed in different media is as follows:

Cooked meat—Turbid growth at first, becoming flocculent in 48 hours.

No change in color of the meat particles, no gas, and no digestion.

Coagulated egg—Flocculent growth, no gas, no digestion.

Egg fluid—No gas, no coagulation or digestion.

Brom cresol purple milk—Slight acidity at first, becoming enough to cause coagulation 15 days. No digestion.

Gelatin—Liquefaction in 10 to 14 days.

Liver broth—Fairly heavy growth with considerable gas produced.

Glucose, 1 per cent, broth—Slight growth and only a bubble of gas formed.

Liver agar and glucose agar shake tubes—Colonies fluffy with a more dense center and some gas production.

Carbohydrates—The organism ferments dextrose, levulose, maltose, dextrin, glycerin, adonite, and inosite, with the production of acid and gas. The reaction in adonite is to be especially noted, as it distinguishes this strain from the non-proteolytic American strain.

American Type A Strain. In the literature there has been some discussion as to whether pure cultures of the American strains of *Bacillus botulinus* are proteolytic or not. This question was answered by Kahn (14) who showed definitely that cultures isolated by the single cell method were proteolytic, and in view of this work there seems now to be no reason to question this fact.

The organisms of type A are large, thick, anaerobic bacilli with rounded ends, occurring singly, paired, and sometimes in chains. The spores are usually subterminal, but a few are medially situated, and as the spore is formed the whole rod is swollen. Detached spores are oval. Stained by Gram's method the young organisms are Gram-positive, but in meat cultures this property is soon lost. In the hanging drop active motility is exhibited. On all protein containing media a pro-

found digestive action is exerted, accompanied by gas production and usually a foul odor. In detail the reactions follow:

Cooked meat—Turbid growth and darkening of the supernatant fluid.

The meat particles are dark red, comminuted, softened, and there is 40-60 per cent digestion, accompanied by gas production in 15 days.

Coagulated egg—In 3 days the cube of egg albumin has noticeably rounded edges and is more or less transparent. The digested portion settles to the bottom of the tube as a flocculent precipitate and considerable gas is formed.

Egg fluid—The reaction in this medium is fairly characteristic. At first the medium is curdled and a cylinder of the curd is formed which is partly digested, but no gas is produced.

Brom cresol purple milk—The casein is usually precipitated in 48 hours and is noticeably digested in 3 days. Some acid and gas is formed and the supernatant fluid ranges from amber to brown in color.

Gelatin—This medium is rapidly attacked with gas production and liquefaction in 4 days.

Liver broth—The growth is heavy and turbid and 40-90 per cent of gas is formed.

Glucose, 1 per cent, broth—Growth is luxuriant, with 20-100 per cent gas in 7 days.

Liver agar and glucose shake cultures—The colonies are discoidal, compact, with definite outline and a small opaque knot or "nucleus" at the periphery. Gas is formed.

Carbohydrates—The organisms of this type ferment dextrose, levulose, maltose, dextrin, glycerin, and salicin, with the production of acid and gas. The formation of acid in salicin seems to be distinctive of this type.

American Type B Strain. The organisms of this type are only slightly different morphologically and culturally from those of type A. They seem to be slightly more actively proteolytic and salicin is not fermented. In glucose and liver agar shake cultures a tendency to form a woolly colony may also be noted.

From the standpoint of virulence there may be a slight difference between type A and type B as Graham and Schwarze (15), Hart and Hayes (16) and Bengtson (13) have observed that a smaller amount of type B toxin is required to produce an intoxication in experimental animals than is necessary when the toxin of type A was used.

American Type C Strain. The organisms belonging to this type differ distinctly in their cultural characters from the other American strains, but produce a symptom complex in animals that is indistinguishable from that produced by the type A and B organisms. The most outstanding difference is the non-proteolytic character of the type C strain.

Like the other types of *Bacillus botulinus*, the type C organisms are anaerobic spore-forming bacilli, but the individual rods of this type are longer and more slender than those of either type A or B and the spores are distinctly terminal. As in the other types, the spore is somewhat wider than the rod and when detached is oval. These organisms appear singly, in pairs, or in chains, are Gram-positive in 7 to 8 hour cultures, although they stain with difficulty even after but 24 hours. Not infrequently they have granular or barred cytoplasm. Motility is observed in very young cultures, but is very slight even in these and is soon lost entirely. In the cultivation of these organisms media containing liver are especially favorable. The reactions in various media follow:

Cooked meat—In this medium there is good growth; the supernatant fluid is at first turbid but soon clears; there is no change in the consistency of the medium and no trace of digestion, although the meat particles may be slightly reddened and there is considerable gas produced.

Coagulated egg—Growth is good, but there is no gas produced and no attack upon the egg cube itself.

Egg fluid—The reaction in this medium is quite different from that exhibited by the strains previously mentioned, as there is no coagulation of the medium, no precipitation, no gas production, and no digestion.

Brom cresol purple milk—The medium becomes slowly acid until there is acid coagulation in about 15 days. There is no precipitation or digestion of the casein.

Gelatin—In 10 to 12 days there is liquefaction and there may be a bubble of gas formed.

Liver broth—There is good growth with 5 to 10 per cent gas production in 7 days in this medium.

Glucose, 1 per cent broth—Growth is frequently difficult to obtain in this medium and when observed it is slight and flocculent. There is no gas production.

Liver agar and glucose shake cultures—The colonies in this medium are diffuse and have no compact nucleus. There is no, or at most, very little gas production.

Carbohydrates—These cultures attack dextrose, galactose, maltose, inosite, levulose, glycerin, and dextrin, with the production of acid and more or less gas.

From the above descriptions it will be seen that the modern strains of *Bacillus botulinus* differ quite markedly from the organism as described by van Ermengem. The most outstanding feature in this regard is the high degree of proteolytic power possessed by the American types A and B. Between these types there seems to be a difference also, as type B cul-

TABLE II

	GALACTOSE	ADONITE	INOSITE	SALICIN
Type A.....{	7.1	7.1	7.1	6.0
	++b	++b	++b	++1.2
Type B.....{	7.0	7.0	7.0	7.0
	+++b	++b	++b	++0.1
Type C.....{	6.1	7.4	5.5	7.4
	++2.0	≠	++b	≠
Lister No. 94.....{	7.0	6.0	5.8	7.4
	+b	++1.3	++b	≠

*Differential fermentation of carbohydrates by *Bacillus botulinus**

The upper row of figures indicates the reaction in pH after 4 days' incubation.

The figures in the lower row indicate inches of gas; b signifies a bubble of gas.

The vigor of growth is indicated by +++ for heavy growth, ++ for moderately heavy growth, + for fair growth, ≠ for slight growth.

tures are somewhat more proteolytic and virulent than those of type A. This difference in activity is hardly sufficient to use as a basis of differentiation as it is a difference of degree and not of kind. On the other hand, when the carbohydrate reactions are considered, it appears that the active fermentation of salicin, with the production of gas and acid, is distinctive of type A, while equally significant is the attack on galactose and inosite by the strains of type C.

The Lister No. 94 strain resembles the type A and B strains in its reaction on dextrin, but it also ferments inosite and therefore resembles the type C strains as well. However, it has its own peculiarity, in that it attacks adonite with the production of acid and gas.

No distinct fermentation reaction can be given for the organisms of type B, but we may tentatively conclude that a culture belongs to this type if it fails to ferment salicin, galactose, or inosite.

The above differential characters in carbohydrate media are given in Table II.

The true value of these reactions in the differentiation of cultures remains to be demonstrated. By far the best method of identification is, of course, by means of inoculation tests, in which guinea-pigs or mice protected with antitoxin of the different types are subsequently injected with a filtrate of the unknown material; the surviving animals indicate the type of toxin injected.

PROPERTIES OF *BACILLUS BOTULINUS* TOXIN

In a consideration of the toxins produced by the various types of *Bacillus botulinus* one is confronted with a situation that is unique in bacteriology. Here we have a group of closely related organisms producing extra-cellular toxic substances all of which give rise to the same symptoms and pathological picture and yet each is absolutely specific from the standpoint of neutralization by antitoxin. That is, each toxin is neutralized by its own specific antitoxin and is not influenced at all by the antitoxin of any other organism belonging to the group. This is quite contrary to the situation observed in the case of other toxicogenic organisms. For example, in the case of *Bacillus diphtheriae* and *Bacillus tetani* it is well known that there are numerous varieties of each of these organisms all of which produce the same symptoms and pathology. Yet a single antitoxin neutralizes the toxins produced by all members of either species.

Effects of physical agents on the toxin. Those physical agents

concerned in the alterations of toxin are light, air, temperature, moisture, and to a lesser degree, the reaction of the toxin and its composition with regard to impurities derived from the medium in which it is produced, although strictly speaking, the latter are chemical factors. Obviously it is impossible to isolate the effects produced by any one of these factors and the deterioration of toxin must be regarded as resulting from the interaction of several factors at once.

In general toxins in the fluid state deteriorate most rapidly when exposed to the action of light and air, but when kept sealed and in the dark, they retain their potency for a much longer period. The filtrate of the ham from which van Er-mengem (2) isolated *Bacillus botulinus* originally, when stored in a sealed container in the dark, did not lose its toxicity in more than eight months, while the toxin produced by pure cultures deteriorated very noticeably in about two months. Furthermore it was noted that toxin retained its potency for months when evaporated rapidly in a desiccator at body temperature, while that allowed to evaporate slowly, with a large surface area exposed to the air at room temperature, lost its potency almost immediately.

Other investigators, notably Brieger and Kempner (17), have found dried toxin to be quite stable if kept in the dark, even though exposed to the air, while Thom, Edmondson and Gilt-ner (18) found that exposure of forty hours to direct sunlight was required to break down the toxin. More recently a study of the effect of light and air on the deterioration of the toxins of the various strains has been made by Bengtson (13) using both fluid and precipitated toxins. The fluid toxins were kept sealed in tubes offering a small surface exposure and at a temperature of about 15°C. The results of such storage, as indicated by the increase in the minimal lethal dose, showed that there was a slow but continued deterioration of the toxin, so that at the end of eight months about five times as much toxin was required to cause the death of experimental animals as had been used originally; while in thirty-three months about

twenty times as much toxin was needed. During this investigation it was also determined that the most rapid change takes place in the toxin during the first few days of storage and that after about ten to fourteen days it becomes more stable. Further tests in which precipitated toxins stored at 15°C. *in vacuo* in the dark were used indicated no breaking down of the toxin in sixty days. Other tests made to observe the effect of room temperature, body temperature, diffuse and direct sunlight, gave similar results although there was some deterioration under exposure to direct sunlight.

Effects of chemical reagents on the toxin. Van Ermengem (2) and Brieger and Kempner (17) found that the toxin of *Bacillus botulinus* was precipitated by tannin, lead acetate, zinc chloride and various neutral salts, and that it lost some of its activity by such procedure, while its potency was completely lost when it was precipitated by the metallic salts, such as gold, platinum, or mercury chloride. They also found it very resistant to reducing agents such as sodium amalgam, but very easily dissociated by oxidizing substances as well as by alcohol and ether. The early experiments with amyl alcohol, as reported by van Ermengem, indicated no deterioration of the toxin, but more recently Schübel, (19), Armstrong, Story and Scott (20), and Bronfenbrenner and Schlesinger (21) have found that the action of ethyl alcohol served to weaken the toxin very noticeably.

The effect of varying concentrations of salt on the production of toxin seems to indicate that all strains produce their toxin in concentrations up to about 6 per cent, but that there is some difference in tolerance of salt among the various strains. Van Ermengem (2) states that his strain was inhibited in 6 per cent salt, while Wyant and Normington (22) observed that all their strains grew in concentrations of 10 per cent. Thom, Edmondson, and Giltner (18) report that their strain grew in 5 per cent salt but not in 8.

Varying concentrations of sugar have been tested for their

effect on toxin production by *Bacillus botulinus* with the result that Dickson, Burke, and Ward (23) found that concentrations of cane sugar up to 64 per cent did not prevent toxin production; Thom, Edmondson and Giltner (18) observed toxin formation in tubes containing 35 per cent of glucose, but not in those with 45 per cent.

A great variety of substances, including olive oil, butter, milk, liquid petrolatum, brain, sugar, egg white, egg-yolk, liquid soap, gelatin and alcohol, have been tested in efforts to find some substance that might be of use in the non-specific treatment of botulism, but the results have not been very encouraging. Burke, Elder, and Pischel (24) found that by mixing certain of these substances, as olive oil, with toxin, and then giving the mixture by injection or by the mouth, the fatal termination of the intoxication could be delayed. This effect was apparently due to slowing up of the process of absorption. In this connection, it is of interest to note that Bronfenbrenner and Schlesinger (25) found that alcohol administered by mouth to guinea-pigs, after they had been given a fatal dose of toxin *per os*, prevented their death, but that when given hypodermically it had no effect on the course of the intoxication.

Acids cause little or no deterioration of the toxin, but seem to have an intensifying action. In his pioneer work, van Ermengem (2) found that from 1 to 3 per cent of tartaric and lactic acid, or 0.5 to 1 per cent of hydrochloric acid, did not alter the potency of a filtrate, even after thirty-six hours' incubation at 35°C. More recently other investigators, notably Bronfenbrenner and Schlesinger (25) and Bengtson (13), have found that toxin maintained at a reaction of pH 4.0, which is that of the stomach, not only maintained its titre but increased its potency. In contrast to these observations Geiger and Gouwens (26) found that the toxins of four strains of *Bacillus botulinus* were not increased in potency whatever, when exposed to hydrochloric acid-sodium citrate or acetic acid-sodium acetate mixtures.

Alkalies have always been known to exert a harmful effect on the toxin as was first noted by van Ermengem (2), who found that concentration of 0.5 to 3.0 per cent of sodium bicarbonate, or 0.5 to 1.0 per cent of ammonia, when allowed to act on the toxin for twenty-four to forty-eight hours, rendered it entirely impotent in amounts as large as one hundred times the minimal lethal dose. Bronfenbrenner and Schlesinger (25) have confirmed these observations.

ILLUSTRATIVE OUTBREAKS

Outbreak 1. At Canton, Ohio (20) in August, 1919, ripe olives were served to a party of eighteen people. When the container was opened it was observed by a waiter that the vacuum had been lost and that the fruit did not "taste right." When served, it was noted by the chef, two waiters, and several guests that the olives "bit the tongue," "seemed to pucker the mouth," or "smelled like limburger." Of those who ate or tasted portions of the fruit all but three developed typical symptoms of botulism, and the severity of the intoxication and rapidity of death seem to have been directly referable to the amount of fruit ingested. Of the fourteen victims, eight of whom were men and six women, four men and three women died.

In one case the first symptoms occurred within a few hours; in six, during the first day; in three, on the second day; in two, on the third day; and in one, on the fourth day after the meal at which the olives were eaten. Of those cases resulting fatally four died on the third day, two on the fourth, and one on the eighth day after the fatal meal. Chemical examination of the viscera in two cases did not indicate the presence of any chemical poison. Bacteriological examination indicated the presence of *botulinus* toxin in the brine from the bottle of olives and viable *Bacillus botulinus*, type A. It was later shown that olives of this same pack were responsible for two other outbreaks.

Outbreak 2. At Grand Rapids, Michigan (27), in January,

1921, canned spinach was served to a group of men and women, of whom twenty-nine individuals, twenty-three women and six men, developed typical symptoms of botulism and three died. In this epidemic it is said that the food gave no indication of spoilage by either taste or odor, although it was remarked that the taste was a bit "biting." In eighteen cases the first symptoms became evident inside of twenty-four hours; in five, onset occurred during the second day; in two, on the third day; in one, during the fourth; and in two, during the sixth day after consumption of the infected food. The fatalities occurred in two cases on the third day and in one case on the fourth day after ingestion.

The spinach came from a pack in which there was an unusual percentage of spoilage and which was admittedly processed at a temperature considerably below usual. *Bacillus botulinus* type A was isolated from the stool of one of the patients on the eleventh day after the meal and the same organism was also isolated from the contents of a can of spinach of the same lot.

Outbreak 3. At Decatur, Indiana (28) in February, 1918, canned string beans were eaten by seven people, all of whom subsequently developed typical symptoms of botulism and of whom four died. At the time the beans were served it was not noted that they showed signs of spoilage, and it was not until the symptoms developed that they came under suspicion. In two cases the onset occurred within twelve hours; in four, it was within twenty-four hours; and in one, it was delayed two days after the meal. The four fatalities occurred on the fourth, sixth, seventh, and ninth days respectively. Examination of the remnants of the contents of the can showed that the juice surrounding the beans did not contain active toxin, but *Bacillus botulinus* type B was recovered from the spleen of one of the fatal cases.

Outbreak 4. In October, 1914, cottage cheese was shown by Nevin (29) to have caused three fatal cases of food poisoning, which exhibited the characteristic symptoms of botulism.

Bacteriological examination of an emulsion of the cheese revealed the presence of *Bacillus botulinus* type B.

BOTULISM IN ANIMALS

A number of investigators have observed that dogs are susceptible to the toxin of *Bacillus botulinus*, although there is not complete agreement on this point. Van Ermengem (2) reported that 10 to 30 cc. of his culture only caused emaciation and abscess formation, while Thom, Edmondson and Giltner (18) noted that one of their dogs resisted 13,000 guinea-pig minimal lethal doses at one time and 200,000 at another. At the same time these authors report that 5 cc. of toxin was fatal to a dog of 5 kg. weight when injected subcutaneously. Subsequently it was reported by Geiger, Dickson, and Meyer (6) that dogs fed toxin exhibited symptoms of posterior paresis. Buckley and Shippen (30) found dog refractory to cultures when fed as much as 30 cc. for from three to four days.

In cats van Ermengem (2) reported that 0.1 to 1.0 cc. of toxin, when injected, produced characteristic symptoms of botulism in from six to eight days, and that the animals eventually died. He considered the experimental intoxication as almost pathognomonic, small subcutaneous doses giving rise to dilatation of the pupils, complete relaxation of the third eyelid, aphonia, aphagia, prolapse of the tongue, secretion of a thick mucus in the nose and mouth, coughing, and suppression of urine and feces.

Goats are very susceptible to the toxin of *Bacillus botulinus* when it is given by mouth or by injection, and van Ermengem (2) found 0.03 cc. a fatal dose.

Geiger, Dickson and Meyer (6) report three outbreaks of poisoning in hogs in which the diagnosis of botulism was supported by bacteriological examination. In two of the outbreaks the animals recovered and *Bacillus botulinus* was isolated from the stools. Graham (31) has also isolated *Bacillus botulinus* frequently from lesions (intestinal?) in pigs and con-

cludes that the organism possesses invasive properties. This conclusion is hardly justified by the evidence and nothing more is indicated than that the organism is not infrequently an inhabitant of the alimentary canal of hogs.

FORAGE POISONING AND BOTULISM IN CATTLE

Thom, Edmondson and Giltner (18) found that cows injected subcutaneously with 8,000 guinea-pig minimal lethal doses of *botulinus* toxin survived, while those given 200,000 minimal lethal doses succumbed. At the same time it was observed that animals fed between 7,000 and 8,000 minimal lethal doses were not affected. Hart and Hayes (16), in their experimental study of botulism in cattle, concluded that these animals could resist large amounts of toxin when taken in through the mouth. Graham and Schwarze (32) somewhat later reported their observations on a large number of cases of toxemia occurring in a herd of cattle fed corn silage. Several animals exhibited symptoms of botulism on two different occasions and four died. *Bacillus botulinus* was subsequently isolated from the silage and the intoxication was attributed to the formation of the poison in the ensilage. A feeding experiment in which animals, both protected and unprotected with antitoxin, were fed *botulinus* toxin did not yield a conclusive result, as one of the unprotected animals did not develop the disease. Seddon, who studied the question of forage poisoning and its relation to bulbar paralysis in cattle in Australia, reported that his toxicogenic organism was toxic for sheep, horses and cattle, but that it was less toxic for cattle than for horses. A dose of 20,000 guinea-pig minimal lethal doses, when injected subcutaneously into a heifer, was fatal, although a dose of 2,000 minimal lethal doses was resisted. The organism studied by Seddon is not at all similar to the American types A and B of *Bacillus botulinus* although it is very much like the American type C organism in its cultural characteristics and may be a representative of this type.

Before leaving this phase of the subject, the observations of Meyer (33) on a disease of cattle in California and Nevada, may be recalled. This disease was characterized by a hemolytic jaundice, hemoglobinuria, and anemic infarcts in the liver. A number of types of anaerobic bacteria were obtained from the lesions in the liver. At this point the investigation was given up by Meyer, but was continued by Records and Vawter (34) and *Bacillus botulinus* was isolated from the liver lesions; lymph-nodes, intestinal wall and intestinal contents of an animal that exhibited the typical ictero-hemoglobinuria. Cultures of this organism were also obtained from cow droppings and hay from a stack on the same ranch. The organism was also isolated from the tissues of two other cows dead of a disease characterized by ictero-hemoglobinuria and distantly removed from the other cases. Subsequently Records and Vawter (34) were unable to confirm these findings in several other cases of this disease and the only conclusion that seems justified is that *Bacillus botulinus* is rather frequently an intestinal inhabitant in cattle and that it may invade the tissues during the course of certain other diseases.

BOTULISM IN HORSES AND FORAGE POISONING

Van Ermengem (2) first reported the susceptibility of horses to the toxin of *Bacillus botulinus* and observed that these animals were among those most easily affected by the poison. Buckley and Shippen (30) also observed fatal termination in two experiments in which a donkey succumbed in six days after eating bran impregnated with 0.2 cc. of a three day old culture, and in which a two year old colt died on the third day after consuming hay on which 10 cc. of a four day old culture had been poured. Seddon (35) has noted the susceptibility of horses to the toxin of his strain of organism, while Hart and Hayes (16) have reported that approximately 300 minimal lethal doses for a guinea-pig of type A toxin was fatal to a horse when injected.

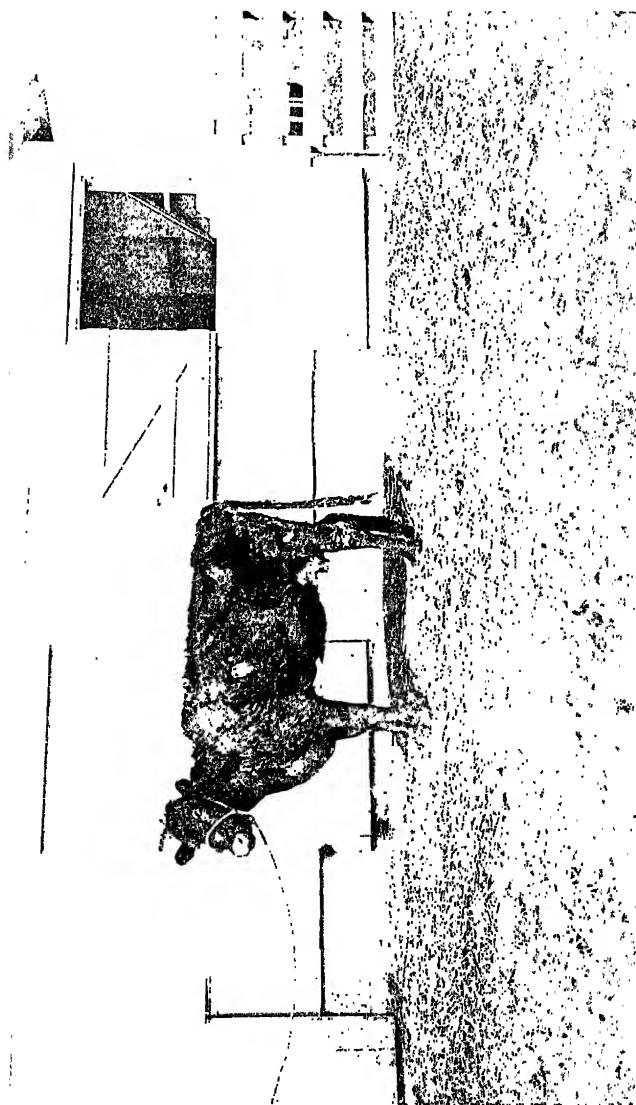


FIG. 7. BOTULISM IN A COW. AFTER GRAHAM.



Of particular interest in connection with the poisoning of horses is the question of intoxication from forage. Geiger and his associates (6) estimated an approximate loss of 3,000 animals in five of the Western States alone during the years 1915 to 1920. They have shown that forage poisoning is by no means rare among horses in the United States, that the disease recurs annually in some localities, that a variety of feeds may be responsible for the disease, and that the rations may appear wholesome and yet be poisonous. As examples of typical equine outbreaks of botulism (forage poisoning) we may cite the reports of Curfmann (36) and Graham, Brueckner and Pontius (37).

Curfmann reported an epidemic of forage poisoning in which five burros died after eating the remnants of material which caused typical human botulism while Graham reported an outbreak with all the symptoms of botulism, among mules that were being fed ensilage. Experimental feeding tests with this silage led to the development of symptoms of forage poisoning in a control animal, while two other horses protected with anti-toxin remained well. Other equine outbreaks have been reported by Graham and Brueckner (37), Rusk and Grindley (38), and Geiger, Dickson and Meyer (6), while Buckley and Shippen (30) have definitely shown that horses and donkeys experimentally intoxicated with the toxin of *Bacillus botulinus* exhibit the symptoms and post mortem findings observed in true forage poisoning.

These definite findings, coupled with the determination that *Bacillus botulinus* was to be found in practically any location in the United States in which it was looked for, have resulted in a tendency to diagnose as botulism many obscure diseases of domestic animals. The inadvisability of this practice is obvious and it seems doubly unfortunate, in view of the experience of Records and Vawter (34), who were able to isolate *Bacillus botulinus* from the tissues of cattle known to have died of other diseases.

At present, the only justifiable conclusion in regard to the

relation of botulism and forage poisoning is that only a tentative diagnosis of equine botulism can be made in any outbreak before experiments have shown the presence of pre-formed botulinus toxin in the food.

LIMBERNECK AND THE QUESTION OF BOTULISM IN BIRDS

Van Ermengem (2) reported that chickens were capable of tolerating extremely large doses of *Bacillus botulinus* toxin while pigeons succumbed to inoculations of 0.1 to 0.5 cc. of toxin. Recently the question of the susceptibility of chickens to the toxin of *Bacillus botulinus* has led to considerable discussion as attention has been called by Dickson (39) and Buckley and Shippen (30) to the similarity of the disease "limberneck" in poultry and botulism in man.

Dickson was the first to call attention to the fact that a toxemic syndrome was produced in chickens after consumption of spoiled food containing the toxin of *Bacillus botulinus*. The most outstanding feature of the disease was the extreme weakness of the fowls, as evidenced by the dropping wings and the decumbent position. Such birds were unable to lift their heads off the ground and it was because of this feature that the disease came to be called "limberneck." Graham and Schwarze (15), assuming that only one type of *Bacillus botulinus* gave rise to typical botulism in fowls, next introduced the term "avian or type A" botulism. Subsequent investigations have shown this to be an ill-founded premise, as all types of the organism give rise to the disease, the difference being quantitative rather than qualitative. Thus Buckley and Shippen (30) found chickens highly refractory to cultures of type B, even when fed as much as 30 cc. daily for several days. Hart and Hayes (16) observed that the subcutaneous inoculation of filtrates of type B produced symptoms of limberneck and eventually death in chickens. But they found it necessary to use 15,000 guinea-pig minimal lethal doses while 400 minimal lethal doses of type A filtrate yielded the same result.

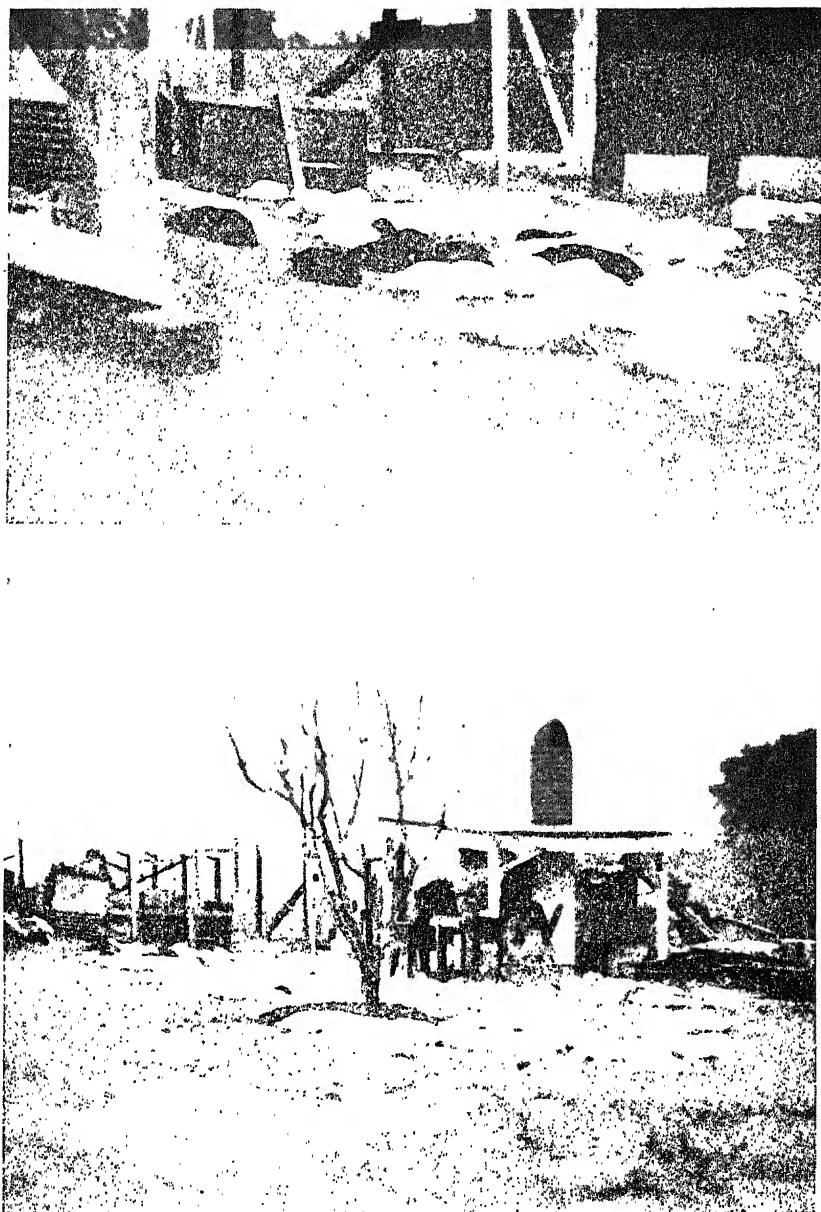


FIG. 8. LIMBERNECK IN CHICKENS. AFTER MEYER

The most recent work of this character is that of Bengtson (13) who tested by inoculation and feeding the toxin of types A, B, and C. Her results indicate only a variation in the number of guinea-pig minimal lethal doses necessary to produce limberneck symptoms and fatalities in chickens, namely, 2,000 for type A, 10,000 for type B, and 25,000 for type C toxin. In feeding tests, the toxicity of the different types appears to maintain about the same ratio.

The only conclusion which can be drawn is that the toxin of any type of this organism may cause limberneck and the final outcome of the attack seems to be doubtful, depending on the amount and the type of toxin ingested.

IDENTIFICATION OF *BACILLUS BOTULINUS* OR THE TYPE OF TOXIN IN INFECTED MATERIAL

The isolation of *Bacillus botulinus* in pure culture from any suspected source may be accomplished by following the technique of Meyer and Geiger (40), in which portions of the food or stool from a patient are emulsified in saline and heated to 60°C. for one hour in order to kill accompanying contaminants. They are then mixed with chopped meat medium, sealed with vaseline, and incubated from ten to twenty days at 37°C. At the end of this time the supernatant fluid in the cultures is removed, centrifuged and inoculated into guinea-pigs protected with the different type antitoxins. In this way the type of toxin produced is determined and confirmation of this may be obtained by the isolation of pure cultures from the chopped meat medium by means of deep glucose agar shake cultures, or by other means of cultivation under anaerobic conditions. In connection with the isolation of the organism from the organs in fatal cases, it is of interest to note that Meyer and Geiger (40) were unable to obtain it from spleen culture, while from stools of clinical cases they were able to recover it in six, seven, and eleven days, respectively, after the ingestion of the toxic food.

A method of determining the type of toxin in any spoiled food

is that recommended by Bengtson (41) and Orr (42). In this case, four series of three mice each are used. One series is inoculated with 1.0 cc., 0.5 cc., and 0.1 cc. of the suspected vegetable juice, fruit juice, or meat extract. A second series is protected by preliminary injection of type A antitoxin and two hours later the injections of food extract are given. The third series is protected by type B antitoxin and the fourth series by type C antitoxin. In this way a rapid typing of the toxin present in the suspected material is obtained, as well as a rough determination of its potency. More recently methods of typing the organisms or their toxins in suspected food material have been devised along immunological lines. Thus Kelser (43) found that by using as antigens filtrates of canned vegetables or sausage in which the organism had been grown, it was possible to determine the type of the strain by complement fixation tests. This observation was subsequently confirmed by Starin and Dack (44) although in the hands of Bronfenbrenner and Schlesinger (45) antigenic varieties could not be determined.

THE ACTION OF *BACILLUS BOTULINUS* TOXIN IN THE BODY

Numerous investigations have been undertaken by various workers to ascertain the site and mode of operation of *Bacillus botulinus* toxin in the body. Edmunds and Long (46) have reported a curare-like action on the endings of the motor nerves to the voluntary muscles resulting in more or less paralysis. The phrenic nerves being affected, the respiratory function was involved and the life of the animal was only maintained so long as the accessory muscles were able to function; death eventually resulted from failure of these muscles. Complete paralysis of the motor nerves was not always observed, but the curare-like action was invariably noted in the early fatigue of the nerves, the stimulation of which would result in a motor response. At the time these observations were made other nerves were mentioned as involved, especially the vagus, and it was indicated that all the clinical symptoms of botulism, which are

purely motor in character, might be accounted for by this peripheral action of the toxin although it was recognized that there might be some action on the central nervous system as well. Schübel (11) has demonstrated a curare-like action of the toxin but has further noted degenerative alterations in the spinal cord. These degenerative changes were not found by Dickson and Shevky (47) in warm-blood animals, but they did observe a marked susceptibility to fatigue in the endings of the motor nerves.

In a later paper Edmunds and Keiper (5) reported the results of further research on the action of *Bacillus botulinus* toxin and correlate their findings with the observations of other workers. They emphasize that it seems hardly necessary to fall back on some of the complicated explanations that have been advanced. They see no reason for believing, as Schübel does, that split products of the normal constituents of nerve cells act on the motor endings, but are inclined to believe that the toxin itself may be responsible for changes in the nerve cells. Finally they have attempted to show that there is no real antagonism between their view and that of Dickson and Shevky by pointing out that the greater or less degree of paralysis of the motor nerve endings observed by them corresponds to the marked susceptibility to fatigue reported by Dickson and Shevky, as the action of curare in its early stages is generally recognized as appearing with the same symptoms as physiologic fatigue. In support of this view they quote Cushny (48) in his discussion of curare, as follows: "Here perhaps better than elsewhere, it can be shown that the condition of paralysis produced by poison is analogous to that termed by physiologists fatigue;" and again he says, "The paralysis of the nerve terminations by curare then is of the same nature as physiological fatigue."

PRODUCTION AND USE OF BACILLUS BOTULINUS ANTITOXIN

The early work on the production of an antitoxin for the toxin of *Bacillus botulinus* was done by Kempner (49) and Fors-

mann (50) and goats were used in which to produce it. Leuchs (51) later introduced the use of horses for this purpose and demonstrated the specificity of the antitoxin produced against the type of toxin used in the immunization. For experimental purposes fairly potent antitoxins may be produced in rabbits and guinea-pigs, but in its production on a commercial scale larger animals, such as goats and horses, are habitually used.

Kempner and Pollack (52) were the first to demonstrate the curative value of *Bacillus botulinus* antitoxin. These investigators found that the serum, when subcutaneously injected into guinea-pigs, even after the appearance of symptoms of intoxication, enabled some of these animals to recover while in other cases fatal termination of the disease was postponed some weeks or even months. Thus a certain degree of prophylactic value for the antitoxin was also established. Confirmation of this work was subsequently obtained by Forsmann and Leuchs and it was further noted that the efficacy of the antitoxin varied with the mode of administration. Numerous other workers have observed that the length of time elapsing between the ingestion of the toxin and the administration of the antitoxin has a decided influence on the effectiveness of the antitoxin.

Due to the more or less prolonged period after the consumption of toxic material before any symptoms appear, a number of investigations have been made with the idea in mind of finding some way of delaying the absorption of toxin so as to increase the chances of a favorable outcome when antitoxin could be obtained. With this in view, Bronfenbrenner and Weiss (53) studied the effect of anesthesia and sedatives on the therapy of experimental botulism, and determined that in animals placed under ether anesthesia, following injection of toxin, the intoxication proceeds more slowly and their lives may be prolonged, even after the appearance of symptoms, by a period equal to that during which the anesthetic is continued. When the anesthesia is discontinued the intoxication proceeds at the usual rate, and ether apparently has no alter-

ative effect on the toxin or mechanism of intoxication. Other substances, such as luminal sodium, nitrous oxide-oxygen mixture or morphine, gave similar results.

The curative value of antitoxin in human cases of botulism has not been definitely established, but there is some evidence that it may be employed effectively in prophylactic doses. The curative property depends on the elapsed time since the ingestion of the toxic food and the amount of toxin consumed. That there may be ascribed to the antitoxin a certain therapeutic value appears to be true from the reports in which it has been used, notably that of Beall (54) although at the present time it cannot be definitely said that human lives have been saved by such methods.

From these considerations the use of antitoxin is certainly indicated in those outbreaks of botulism in which numbers of persons have eaten the toxic food and in which the diagnosis is perfectly clear in some cases while other persons are still symptomless or are exhibiting only the first signs of intoxication. In such instances it should be borne in mind that it is the only known specific.

The administration of antitoxin should be by intravenous injection of large quantities, according to Dickson and Howitt (55), using the customary intracutaneous tests to determine hypersensitivity to horse serum. When no sensitivity is observed, the intravenous injection of antitoxin should begin at once and continue at the rate of not more than 1 cc. per minute until the full amount is given. When hypersensitivity is observed, preliminary desensitization by repeated subcutaneous or intramuscular injection of 1 cc. at one-hour intervals should be carried out. One hour after the last injection the prophylactic doses is given at a very slow rate by intravenous injection.

The method followed in England for the use of antitoxin is given in the following instructions issued by the Ministry of Health (56).

"1. *Immediate administration.* The only remedy at present known for botulism is botulinus antitoxin given by injection and even this is unlikely to save life if the disease has progressed to a late stage. It is, therefore, of the greatest importance to give the antitoxin at the earliest possible moment—i.e., as soon as the earliest symptoms of blurred or double vision, giddiness, ptosis, difficulty in speech or swallowing suggest the diagnosis of botulism.

"2. *Method.* The effectiveness of treatment by antitoxin for botulism is so greatly increased by intravenous injection that this method of administration should always be employed (otherwise the intramuscular method should be used). The risk of serious symptoms arising in persons highly sensitive to horse serum must be recognized, and when, in the judgment of the medical practitioner, such is likely to be great, he should administer a preliminary injection of a small quantity of the antitoxin (0.5 cc. equals 8 minims) *subcutaneously*. If this produces clear evidence that the patient is sensitive (that is, if a reaction appears in half an hour) then the antitoxin must be given with particular caution, the first intravenous injection consisting of 0.5 cc. of antitoxin being diluted with 50 cc. of saline, and subsequent injections being diluted less and less till the full dose had been administered.

"3. *Dose.* Only large doses will save acute cases. The intravenous dose should be from 20 to 50 cc. of the antitoxin, previously warmed to body temperature and injected very slowly; this amount may be repeated daily if necessary.

"*Note.* All other persons who have consumed the suspected food but have not yet presented symptoms should be given a prophylactic dose of antitoxin (i.e., 10 cc.) intramuscularly, to be followed by larger doses intravenously should symptoms appear."

The State Department of Health of New York distributes on special request monovalent botulinus antitoxic sera, Types A and B, and issues with the sera the following statement as to their use:

"Serum therapy in cases of human botulism has not been used sufficiently to warrant a definite statement as to its value, that is, how early the serum must be given to be effective or how late its injection would be useless. Experiments with animals indicate that the serum may be of value when given within 24-48 hours after the ingestion of the food containing the toxin. Two types of the bacillus have been recognized. They produce different toxins. Since the immediate determination of the type is not practical, a polyvalent serum of both types of monovalent serums, A and B, should be given. The two monovalent serums may be combined or given separately. Theoretically, on account of the exceptionally high titre of the A serum, relatively larger doses of B serum should be given.

"Administration of serum

"The serums are distributed in bottles containing 20 cc. From 40-80 cc. of the serum should be given intravenously by gravity at the earliest possible moment.

"In order to safeguard against severe reactions of an anaphylactic character in persons highly sensitive to horse serum, the usual precautions of desensitizing the patient should be carefully observed."

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CHAPTER VIII

MUSHROOM POISONING

Introduction. Types of mushroom poisoning. Classification of mushroom poisoning. Differentiation between edible and poisonous fungi. I. *Poisoning by Amanita phalloides*. Introduction. Symptomatology and diagnosis. Illustrative cases. Pathologic lesions in *Amanita phalloides* poisoning. Action of *Amanita phalloides* poison on animals. The toxic principle of *Amanita phalloides*. II. *Poisoning by Amanita muscaria*. Introduction. Symptomatology and diagnosis. Illustrative cases. Pathologic lesions in *Amanita muscaria* poisoning. Action of *Amanita muscaria* poison on animals. The toxic principle of *Amanita muscaria*. Chemical nature of the toxic principle in *Amanita muscaria*. Physiological action of the poisonous principle. III. *Miscellaneous mushroom intoxications*. IV. *Treatment of mushroom poisoning*. *Amanita phalloides* poisoning. *Amanita muscaria* poisoning.

INTRODUCTION

Mushroom poisoning or mycetismus, which, of course, is an intoxication, is a distinct type of food poisoning. Although by no means as frequent in occurrence as food poisoning of bacterial origin, it nevertheless appears that several hundred cases are observed each year and that the mortality rate is quite high.

One of the earliest recorded instances of mushroom poisoning occurred in the family of the Greek poet Euripides and resulted in the death of the poet's wife, daughter, and two sons.

Among the early investigators of this subject Paulet, making a statistical study of the frequency of mushroom poisoning in France, found that between 1749 and 1788 there were at least 100 deaths, in the environs of Paris alone, that might be attributed to this cause. A little later, Guillaud (1) estimated that mushroom poisoning was responsible for the loss of about 100 lives annually in the south of France. Inoko (2), in 1887, compiled the statistics of mushroom poisoning in Japan during

an eight year period, and found that over 480 cases had been reported. Among these 480 cases 103 resulted fatally. Similar statistics collected by Ford (3) in 1907 from the English and German literature, and from the French literature after 1900, indicated the occurrence of 235 cases of mushroom intoxication. Subsequently Ford (4), showed that approximately 1,000 cases with 318 deaths and 171 cases with 49 deaths had been recorded in the medical literature of France, and Germany and Austria respectively. The occurrence of mushroom poisoning in Japan has been recently reported by Ichimura (5).

In America, Cheney (6), in 1871, appears to have been among the first to report instances of mushroom intoxication, while McGlenn (7) and Kessler (8) soon afterward reported similar observations. However, the occurrence of any considerable numbers of cases annually seems not to have been recognized much before the end of the first decade of the present century. Since this date Ford (4) has reported the occurrence of at least 217 authentic cases with about 91 deaths.

TYPES OF MUSHROOM POISONING

Of recent years the frequency of intoxication due to the ingestion of poisonous fungi has attracted considerable attention and our information regarding the poisonous species has been greatly increased as the result of the efforts of many investigators. At present it may be said that we have accurate knowledge of about 80 such species, some of which are poisonous to man when ingested and others of which produce symptoms in animals only, on inoculation.

As the result of extensive studies made to determine the effect of various species upon the animal body we now know something about the action of the intoxicating principles in these fungi. For example, it is now recognized that in certain instances the action of the principle is to set up an acute irritation of the gastro-intestinal mucosa, in other instances the action is upon the nerve centers, while in others there may be a stimu-

lation of the terminal filaments of the nerve fibers or a direct action upon the cells of certain organs. But in any individual case of mushroom intoxication the patient usually presents a picture that is somewhat less sharply defined than the preceding statement would imply, as quite frequently gastro-intestinal and nervous symptoms or gastro-intestinal disturbance accompanied by degenerative alterations in the cells is observed. In fact, it can almost be taken as axiomatic that in mushroom poisoning there will always be gastro-intestinal disturbance accompanied by other symptoms although at present it cannot be definitely decided as to whether it is due to the poisons of the fungi or to some other irritating principle.

CLASSIFICATION OF MUSHROOM POISONING

Until comparatively recently the classification of mushroom poisoning most generally accepted has been that proposed by Huseman (9), in which three types of intoxication are distinguished, namely, *mycetismus intestinalis*; *mycetismus cholericiformis*; and *mycetismus cerebralis*. At the time it was proposed, such a grouping of the different types of cases was quite satisfactory but in the light of our present knowledge of the subject the inadequacy of such a classification is obvious. Consequently, a grouping based on the latest available information has been proposed by Ford (4) and is the one followed in this chapter. In this classification Ford distinguishes five types of poisoning that can be fairly readily distinguished on the basis of the symptoms observed.

1. *Mycetismus gastro-intestinalis*. The transitory character of the extreme nausea and diarrhea is the outstanding feature of this type of case and fatalities among patients exhibiting such symptoms are rare. The principal species of fungi responsible for such poisoning are: *Russula emetica*, *Boletus satanas*, *Boletus miniato-olivaceus*, *Lactarius torminosus*, *Entoloma lividum*, and *Lepiota morgani*.

2. *Mycetismus cholericiformis*. In this intoxication the symptoms are at first gastro-intestinal followed somewhat later by

loss of strength and weight, paroxysms of pain, nephritis and anuria, delirium and coma. The mortality rate among such patients is quite high, approximately 50 per cent of the cases terminating fatally. *Amanita phalloides*, *Pholiota autumnalis*, and *Hygrophorus conicus*, are the species giving rise to this type of intoxication.

3. *Mycetismus nervosus*. Salivation and excessive sweating are the outstanding features of mushroom poisoning of this character. In the early stages of the intoxication violent gastro-intestinal symptoms are observed, usually, and are followed by delirium and hallucinations, convulsions and coma. In some cases the alleviation of the symptoms is very rapid and presents a striking contrast to the previous critical condition of the patient.

Mushroom poisoning of this kind occasionally results in death, but in many cases, particularly of the milder sort, there may be simply vomiting and diarrhea or profuse sweating and salivation. This type of mycetismus is produced by those species of fungi only, which contain muscarin or closely related substances. *Amanita muscaria*, *Amanita pantherina*, *Clitocybe illudens*, *Clitocybe sudorifica*, *Inocybe infelix*, *Inocybe infida*, *Inocybe lateraria*, *Inocybe sambucina*, *Inocybe frumentacea*, and *Inocybe repanda*, are the species of mushrooms now recognized as giving rise to poisoning with the above features.

4. *Mycetismus sanguinareus*. Gastro-intestinal symptoms followed by jaundice, anemia, and soon afterward by hemoglobinuria distinguish this intoxication from the types mentioned above. *Helvella esculenta* is the only species of fungus definitely known to give rise to poisoning involving this syndrome although there is some evidence that *Morchella esculenta* may also be implicated. The presence of a resistant haemolytic poison in the fungus is responsible for the blood destruction resulting in the coffee-brown urine. The mortality rate is notably low in such cases as these, although fatalities do occur.

5. *Mycetismus cerebralis*. Transient cerebral symptoms consisting of excitement and hallucinations are the outstanding

features of these cases. The pupils of the eyes are dilated and in some instances the patients collapse, but recovery from poisoning of this type is almost invariable. *Panaeolus campanulatus*, and *Panaeolus papilionaceus* are the only species to which this sort of intoxication can be definitely attributed although *Coprinus narcoticus* may also give rise to similar symptoms.

DIFFERENTIATION BETWEEN EDIBLE AND POISONOUS FUNGI

Some species of mushrooms contain poisonous principles, while others do not, and are commonly recognized as edible. Unfortunately, there are no simple tests by which the layman may distinguish the poisonous from the harmless species. In this connection it cannot be too strongly emphasized that such commonly applied tests as peeling the top or pileus or cooking with a silver spoon are worthless as indicating the innocuous or poisonous varieties, nor can any more confidence be placed in the taste of the fungi, as some of the most poisonous mushrooms have an agreeable or even delicious flavor. The only safe rule, for those who are fond of mushrooms to follow then, is for them to really study the subject and learn the distinguishing features of the edible species and to *collect these only*. No departure from this rule should ever be permitted and no experiments with new or unfamiliar varieties should ever be undertaken. The great importance of strict adherence to such a policy will be obvious when it is understood that there are more than 80 species growing in America, alone, that are known to be poisonous.

This warning against the indiscriminate consumption of mushrooms should not be construed as indicating the wisdom of entirely denying oneself the enjoyment of these delicacies, however, as the number of edible species is really large, and recognition of a few surely harmless varieties is comparatively easy and may be practiced with certainty.

I. POISONING BY AMANITA PHALLOIDES

Mycetismus chloreriformis. This species of fungus, which gives rise to the type of poisoning known as *Mycetismus*

choleriformis, is undoubtedly the most frequent cause of mushroom poisoning. In the French and German literature the species has been described under a variety of names such as "l'orange ciguë," "l'orange souris," or "Knollenblätterschwamm," but in England and America it is most often referred to as the "toadstool," or "the deadly amanita."

The relative abundance of the species and its high degree of toxicity no doubt explains the occurrence of the high percentage of poisonings attributed to it. As previously stated the mortality rate among those intoxicated by this species is high. Gillot (10) collected the statistics of 115 cases of poisoning caused by *Amanita phalloides* and found that 73 of the victims died, a mortality rate of 63 per cent; Ford (3) cited 204 cases, with 153 deaths, a mortality rate of 75 per cent; and Roch (11) reported 188 deaths in the series of 381 cases he investigated, a mortality of 49 per cent. This figure, although somewhat lower than that determined by the other investigators, probably represents more accurately the real frequency of death in these cases. Confirmation of this is obtained from the French, Swiss, German and Austrian literature in which 556 cases with 262 deaths and 105 cases with 44 deaths are reported. The fatality rate in these series of cases is 47 and 41.9 per cent respectively.

The susceptibility of young children is noticeably greater than that of adults and they are more likely to succumb to the intoxication, so that the ingestion of only one or two plants, or even of a part of a specimen may result in acute poisoning or death. Thus it will be seen that the mortality rate will vary somewhat according to the amount of the plant consumed and the respective ages of the victims. However, when the fungi happen to be eaten in any large amount acute intoxication followed by death in less than 48 hours is commonly observed. In those cases where poisoning is less severe, the symptoms abate in 6 to 8 days, and normal health and strength are enjoyed by the patient in about a month after the attack. When the patient is even less affected, due to the ingestion of

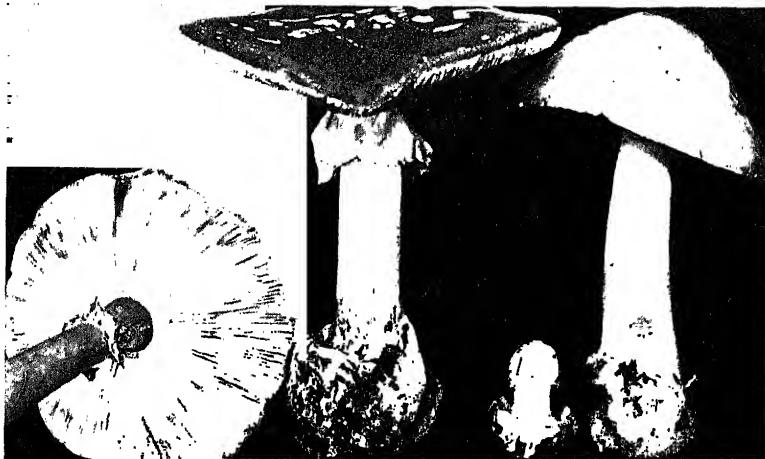


FIG. 9. *AMANITA PHALLOIDES*

Brownish, umber, or olive-brown form (reduced). Caps brownish or whitish, and streaked with brown, scales white, stem slowly turning dull brown where bruised. After Atkinson.

only a very small quantity of the fungus, the symptoms are chiefly indicative of violent gastro-intestinal disturbance. In such cases the symptoms may subside very rapidly and the patient may be entirely recovered within a few days.

Symptomatology and diagnosis. Following a prodromal period of 6 to 15 hours, symptoms which are distinct and quite characteristic of poisoning by *Amanita phalloides*, appear. Acute abdominal pains, vomiting and diarrhea are always observed. The vomitus and stools are seen to contain more or less undigested food, blood, and mucus. In a few cases constipation has been observed; frequently anuria occurs, although in general the urine is straw-colored, untinged with hemoglobin. Periods of remission often follow the periods of pain and vomiting, but are of short duration. In the course of the paroxysms of pain it is common to observe the "Hippocratic facies," or "la face vulteuse," of the French authors. Within a day or two jaundice, cyanosis, and coldness of the skin, especially of the extremities, develops. In those cases resulting fatally the patients frequently relapse into a comatose condition from which it is impossible to rouse them. In this type of mushroom intoxication nervous and mental symptoms occasionally occur but it is chiefly in children that convulsions are observed and in adults only as a terminal event. No ocular symptoms are noted as a rule, the pupils remain undilated and continue to react to light and accommodation. During recent years especial attention has been paid to symptoms having their origin in the kidneys and nervous system and tests of renal function by the phenolsulphonphthalein method should be made. Clark, Marshall, and Rowntree (12) studied with particular care one individual who eventually died from chronic intoxication 28 days after eating *Amanita phalloides*. Bleeding from the gums and rectum, a renal function of but 3 per cent in a two-hour period, and at autopsy an epithelial necrosis of the kidney together with a central necrosis of the liver, an acute enteritis and colitis, were the outstanding features of the case. On the basis of these observations, these authors suggested that

the nervous and mental symptoms often observed in such cases might be uremic in nature. In some cases glycosuria may occur.

Illustrative cases. The observations of Pfrom (13) may be taken as typical of the picture usually seen in cases of poisoning by *Amanita phalloides*. An Italian family, living in New Jersey, and consisting of the father, mother, and four children, consumed varying amounts of mushroom stew as a part of their evening meal. The children apparently ate only small portions of the stew while the parents ate large quantities of the fungi. Between five and six hours later the first symptoms of poisoning developed, consisting of vomiting, abdominal pain, thirst, headache, and constipation. By 7 o'clock the next morning the father was cyanotic, prostrated, vomited frequently, and exhibited muscular twitching in the chest. An hour later he was delirious, eyes glazed and pupils contracted. During the day he was somewhat more comfortable, but in the course of the evening the symptoms returned, and paroxysms of pain recurring about every twelve hours were observed. At this point the patient was removed to the hospital where retching and vomiting, pain in the chest, difficult breathing, thirst, frequent attacks of hiccough, contraction of the muscles of the face—"la face vulteuse"—and an uncontrollable diarrhea, with small greenish and bloody stools, were the features of the case at once noted. Soon cyanosis developed and death due to dyspnea occurred on the eighth day after eating the mushrooms. The mother exhibited similar thirst, prostration, vomiting, rapid pulse, and aborted a five months fetus. Cyanosis rapidly developed followed by delirium and coma and death due to cardiac failure closed the case eight days following the meal at which the mushroom stew was eaten. Bloody urine, and a slight fever, with a temperature of 99° to 101°F., were also seen in the course of the case. The children suffered from pain in the abdominal region and vomited frequently but rapidly developed unconsciousness and died in 58 to 59 hours after partaking of the juice only in the stew.

Another typical outbreak of poisoning by *Amanita phalloides* involving six individuals and with four fatalities has been reported by Plowright (14). One of the cases illustrates the danger involved in eating only the smallest quantity of a poisonous fungus. A boy, twelve years of age, ate only one-third of the pileus of a raw plant about 11:30 in the morning. Thirteen hours later, that is, about one o'clock the next morning he began to suffer from vomiting, diarrhea, and great thirst. His condition improved, however, and he was able to eat breakfast, but the vomiting and diarrhea returned soon afterward, followed by a period of remission so that the following morning his condition was much improved. In this way the cycle was repeated until the fifth day when he had slight convulsions and died. In another instance, a boy of five years, ate an unknown quantity of *Amanita phalloides*. Ten to twelve hours later he developed severe diarrhea, abdominal pains, and intense thirst. Soon afterward he became comatose and death ensued on the third day after eating the fungi.

The third instance of intoxication caused by eating *Amanita phalloides*, which Plowright reported, was remarkable for the fact that two of the persons affected were severely poisoned but eventually recovered. In this outbreak a man and wife together with their son and daughter gathered and ate three to four pounds of fungi. The mother and son ate the fungi raw. Early the next morning the mother and son were taken ill, followed somewhat later by the father and daughter. The usual symptoms of diarrhea, vomiting, thirst, profuse sweating, and intense pain in the abdomen in the epigastric region were noted. The boy developed convulsions, distortion of the face muscles, nystagmus, dilatation of the pupils, and died fifty-four hours after eating the mushrooms. The mother developed jaundice on the third day of the poisoning and suffered greatly from pains which were paroxysmal and cramp-like in character. She aborted a three months fetus. On the fourth day she was restless, with retracted head, almost unconscious, with complete anuria, respiration was irregular and of the

Cheyne-Stokes type and she died about one hundred hours after eating the fungi.

The father exhibited the same symptoms of poisoning but on the eighth day felt somewhat better and eventually recovered. The daughter developed diarrhea with mucus and blood in her stools, great thirst and enlargement of the liver. She had no fever, her diarrhea gradually subsided and she slowly recovered.

Pathologic lesions in Amanita phalloides poisoning. The characteristic findings at autopsy in cases of "phalloides" intoxication were first described nearly seventy-five years ago by Maschka (15). He observed the absence of postmortem rigidity, dilation of the pupils, failure of the blood to coagulate, and a cherry-red color, ecchymosis and hemorrhage in the serous membranes and parenchymatous organs. The urinary bladder was observed to be full, and fatty degeneration of the internal organs was also seen, but received only slight attention. Carayon (16), Chouet and Pelissie (17) and Sahli (18) later confirmed, in general, the observations made by Maschka. However, Carayon failed to note any fatty degeneration of the internal organs, while in one case he did observe congestion of the meninges. On the other hand, Sahli observed the gross lesions described by Maschka, including subpleural and intrapulmonary hemorrhages and noted in addition, a general atrophy of the panniculus adiposus. Examination of histological preparations also indicated fatty degeneration of the heart muscle, the liver, the kidneys, the diaphragm, and the voluntary muscles, such as the pectorals, deltoid, the tongue, and the muscles of the abdomen. The striking appearance of so much fat in the liver reminded Sahli strongly of its appearance in acute phosphorous-poisoning and has since led to frequent use of this simile in descriptions of intoxications by *Amanita phalloides*. He also noted congestion of the stomach and intestines, the swollen Peyer's patches and follicles. Handford (19) and Tappeiner (20) have also reported observing the occurrence of similar lesions, and noted the similarity to

phosphorous-poisoning. Estimating the percentage of fat in the liver, in two cases, Tappeiner found 53.6 per cent in one case and 68.9 per cent in the other, as contrasted to 8 to 12 per cent usually found in the liver of normal individuals. Thus it will be seen that the percentage of fat in the liver in cases of *Amanita phalloides* closely approximates that found in phosphorous poisoning, an observation which has been confirmed by Thiemich (21).

Moers (22) subsequently described three cases and noted especially hemorrhages into the stomach and intestines as well as on the surface of the liver and kidney, and in the heart and pericardium, ovary and brain. Chemical examinations made for arsenic, phosphorous, and muscarin, were negative, and in the absence of these substances the lesions may logically be attributed to the ingested mushrooms. Somewhat later, cases were described by Plowright (14) in which the usual symptoms and lesions were seen, but with gangrenous patches in the intestinal mucosa, and in one case a general peritonitis and enlargement of solitary follicles in the intestines.

More recently studies of the pathology of intoxication by *Amanita phalloides* have been made by a number of German investigators. Schürer (23), for example, performed an autopsy on a five-year-old child which had died thirty-five hours after the consumption of some fungi presumed to be *Amanita phalloides*. In this case inflammation of the ileum and colon; swelling of the mesenteric glands; fatty degeneration of the heart and skeletal muscles; fatty degeneration of the liver and kidneys, and advanced degenerative changes in the cells of the central nervous system, were the outstanding features. Schürer considered the fatty degeneration of the liver, kidneys, heart, and skeletal muscles, taken together with the swelling of the follicles and Peyer's patches in the intestines, as pathognomonic of poisoning by this species of fungus.

Fahr (24), reported finding the usual lesions in an autopsy upon a case of "phalloides" intoxication, but on microscopic examination of the organs he observed the presence of doubly

refractive fat (cholesterin esters) in the kidneys. This observation was subsequently confirmed by Prym (25), and it was suggested that the presence of such doubly refractive fat in the liver and kidney might be taken as a point for differential diagnosis between mushroom poisoning and acute yellow atrophy of the liver, or phosphorous poisoning, as singly refracting substances only, are present in the fat in the latter case. Prym also noted an attempt at regeneration in the connective tissue, and in the bile ducts in the older cases.

Herzog (26), has also recorded with great care the lesions he observed in six individuals, who died between three and four days after eating *Amanita phalloides*. In these cases, advanced destruction of the cells in the liver, with fatty infiltration, together with hemorrhages and leukocytic infiltration were noted. However, regeneration of the liver in the nature of reproduction of bile-ducts had begun. Hemorrhages and leukocytic infiltration in the liver were also seen, and a large number of liver cells showing no fatty degeneration were noted to be in an advanced stage of destruction. Such a condition has been described by Paltauf (27) in acute atrophy of the liver. The kidneys, heart muscle, and pancreas all showed fatty degeneration in the cases described by Herzog and there was fatty degeneration and large areas of hemorrhage in the splenic pulp. Herzog considered the lesions in cases of *Amanita phalloides* intoxication as characteristic and the disease as hepatogenous in origin.

Recently Treupel and Rehorn (28) have made an important study of liver function in cases of "phalloides" intoxication.

Summing up the findings of a large number of investigators who have studied the pathology of intoxication by *Amanita phalloides* or the choleric type of mycetismus certain conclusions appear to be obvious. In the first place, the initial symptoms appear to be gastro-intestinal, followed somewhat later by acute abdominal pains, nephritis, anuria, delirium and coma. The poison from the fungi evidently produces wide destruction of cells in the liver, kidneys, central nervous system,

blood vessels, voluntary and involuntary muscles. Such widespread cellular destruction would seem almost to preclude the possibility of recovery from such poisoning, but it is to be remembered that attempts at regeneration in the bile-ducts have been seen by Prym and Herzog and every effort should be exerted to prolong the life of the patient until the effect of the poison has worn off, as such observations indicate that the injury inflicted is not beyond repair.

Action of Amanita phalloides poison on animals. The question as to whether or not there is more than a single poison in *Amanita phalloides*, which may be responsible for the lesions seen in man, can only be resolved by studying the effect of the fungus on experimental animals. Ford (29) has shown that watery extracts of the fungus, when injected subcutaneously into rabbits and guinea-pigs, leads to the death of the animals in a space of time proportional to the amount of the poison injected. At autopsy, an extensive gelatinous edema in the subcutaneous tissues, is seen at the site of the inoculation, and the edematous tissue exhudes a thin, reddish fluid under pressure. The adjacent lymphatic glands are enlarged and hemorrhagic, and small hemorrhages are observed in the neighboring fascia and muscular tissues. The blood-vessels in the abdominal viscera are congested and there are hemorrhages in the liver, kidneys, adrenals, peritoneum, lymphatic glands, pleura and lungs. In female animals, hemorrhage appears also, in the ovaries and uterus. The urine in the bladder is deeply pigmented with blood but there are no intact corpuscles demonstrable even after centrifugation. The contents of the intestine and stomach appear blood-stained and minute ulcers in the intestinal mucosa are observed. Extravasted blood at the base of the ulcers indicates the source of the hemorrhages.

Examination of histological preparations shows that the connective and muscular tissue is much swollen, and that the muscle-fibers have undergone hyaline degeneration. In the lymphatic glands a congested and hemorrhagic condition appears, the lymph cells are necrotic with pyknotic nuclei and

there is an increase of pigment. The spleen contains a noticeably increased amount of blood pigment, and the cells of the splenic pulp are necrotic.

All the organs exhibit fatty degeneration, the fat being especially widely distributed in the liver and kidneys.

From this description of the lesions seen in animals, it appears that the action of the poison in the fungus is quite different from its action in man. It is to be remembered that in animals the lesions are produced as the result of subcutaneous injection of the poison, rather than absorption from the alimentary canal. Neither rabbits nor guinea-pigs appear susceptible to the poison of the fungus when administered by mouth.

There are, however, certain features of the intoxication common to both man and animals. For example, the widespread congestion and hemorrhages, together with the extensive cellular destruction in all the organs and lymphatics, and the fatty degeneration are characteristics in common. On the other hand the extensive blood destruction as shown by the hemoglobinuria is a feature of the poisoning seen only in animals.

It appears then, that in animals we have the characteristic lesions seen in man, and in addition, certain changes, such as the extensive blood destruction, which are not observed in human cases.

The toxic principle of Amanita phalloides. The earliest attempt to obtain the active principle of *Amanita phalloides*, by experimental methods, seems to have been made by Letellier (30), who obtained a substance which he named *Amanitin*. Somewhat later Letellier and Speneux (31) obtained two poisons from another fungus, probably a variety of *Amanita phalloides*. One of these poisons gave rise to vomiting, diarrhea, and inflammation of the alimentary canal in cats, while the other, regarded as a glucosidal alkaloid, was simply narcotic in its action, and was considered identical with the amanitin which Letellier had previously described. Subsequently,

Boudier (32) gave the name *bulbosin* to the active principle of *Amanita phalloides* while Ore (33) called it *phalloidin*.

The next step in the elucidation of the nature of the toxic principle in *Amanita phalloides* was taken by Kobert (34), who observed the important fact that watery and saline extracts of the dried fungus were powerfully hemolytic, and laked the corpuscles of numerous animals in dilutions as high as 1:125,000 of the dried material. Kobert gave the name *phallin* to this substance, and for a time, regarded it as the active principle in the fungi, in spite of its thermolability and its inactivation by weak acids and alcohols. Chemically, Kobert regarded the substance as a toxalbumin, because it contained a small amount of coagulable protein, and somewhat resembled the hemolytic substance produced by certain spiders. Somewhat later, Kobert (35) demonstrated a highly toxic substance in alcoholic extracts of *Amanita phalloides*, and as these extracts yielded precipitates with alkaloidal reagents he concluded that the active principle must be an alkaloid.

Most recently Ford (36) has shown that saline and watery extracts of *Amanita phalloides*, although powerfully hemolytic, lose their hemolytic property when heated to 70°C., or are exposed to the action of weak acids and alkalies, and to the digestive juices, pepsin and pancreatin. However, extracts treated as indicated above, remain highly poisonous to rabbits and guinea-pigs when injected subcutaneously and give rise to lesions in these animals that are almost identical with those seen in man. From these observations Ford concluded that the rôle of the hemolytic principle was at most secondary, and that the active principle is the substance that remains poisonous when the mushrooms are eaten, even after cooking, and after subjection to the action of the chemicals mentioned above.

As an aid to clarity in discussions of *Amanita phalloides* intoxications the hemolytic substance,—the phallin of Kobert—was called by Ford *Amanita hemolysin*, while the non-hemolytic substance remaining in the extracts after heating, was given the name *Amanita toxin*. This latter substance was re-

garded as the active principle responsible for death in man following ingestion of the fungi.

Abel and Ford (37) later showed that treatment of watery extracts of *Amanita phalloides* with methyl alcohol yielded a precipitate which contained the Amanita hemolysin, while the Amanita toxin remained in solution. Examination of the precipitated material showed it to contain a small quantity of coagulable protein, which was removed by the addition of metaphosphoric acid or uranyl acetate. The residual portion of the solution consisted, in large part, of a glucosid which reduced Fehling's solution and ammoniacal silver nitrate, and after hydrolysis with mineral acids, gave a precipitate upon the addition of neutral or basic lead acetate. This precipitate did not ferment with yeast.

On the basis of these and other reactions, Abel and Ford concluded that Amanita hemolysin is not a toxalbumin, but rather a nitrogenous glucosid, which decomposes under the influence of acids, to yield a pentose and volatile bases such as ammonia and methylamin.

Subsequent investigations by Abel and Ford (38) led to the development of a method for the isolation of this glucosid, and it was obtained in a pure state. Such material possessed undiminished hemolytic power and was active in dilution of 1:300,000, but was never regarded by these investigators as the intoxicating principle.

The isolation of Amanita toxin, from alcoholic extracts of the fungus, has been accomplished by Schlesinger and Ford (39) by precipitation with phosphotungstic acid. The removal of accompanying impurities was affected by reagents, such as silver nitrate and basic lead acetate. The toxic material thus obtained did not give the Millon reaction, the Biuret test or react to any of the color tests employed to indicate the presence of alkaloids. It did not precipitate with alkaloidal precipitants, did not reduce Fehling's solution, and was highly resistant to boiling in aqueous or alcoholic solutions. Because of these reactions Schlesinger and Ford did not consider it a glucosid,

an alkaloid, or a protein according to the usual definition of the term. Nitrogen and sulphur—the latter present as conjugate sulphuric acid—were demonstrable in the material, and the odor of amines and indol was given off when it was fused with potassium hydrate. As it also gave the characteristic pyrrole-red test it was concluded that the toxin was either an indol derivative or an aromatic phenol, combined with an amin group, in such a way as to readily form an indol or pyrrol ring.

Whatever the exact chemical nature of the substance may be, the *Amanita* toxin obtained by this technique, when injected into animals gives rise to an acute intoxication. Autopsy of such animals reveals lesions closely resembling those seen in fatal cases of poisoning in man. Particularly noticeable are the hemorrhages, widespread necrosis and fatty degeneration of the cells of the internal organs, particularly in the liver and the kidneys. From the evidence now available it appears that this substance is certainly the active principle in "*phalloides*" intoxication.

From these considerations it would seem, then, that the lesions observed in laboratory animals, when injected with extracts of the raw fungus, represent a combination of the lesions produced by *Amanita* hemolysin and *Amanita* toxin when injected separately. As only part of these lesions are observed in man, when cooked fungi are eaten, it is no doubt true that *Amanita* hemolysin, which is responsible for the widespread destruction of red blood corpuscles, with hemoglobinuria, in animals, is destroyed in the process of cooking.

Finally, the investigations of Rabe (40), who stated that alcoholic solutions of *Amanita phalloides* would stop a frog's heart in diastole, are to be considered. These tests—carried out in a Williams' perfusion apparatus—apparently indicated that the effect of *Amanita* toxin could be neutralized by atropin, which would point to the presence in the fungi of a poison like muscarin. Ford and Brush (41) have since shown that this heart stoppage was due to the salts present in the fungus, and could be relieved by washing out the heart with Ringer

and Locke's solution, as well as with atropin. Thus it is apparently indicated that there is no alkaloidal substance similar to muscarin in *Amanita phalloides*.

From our present knowledge of the subject the active principle in poisoning from this species of fungus, undoubtedly appears to be the Amanita toxin, with Amanita hemolysin playing but a minor part, if any at all, in the intoxication.

II. POISONING BY AMANITA MUSCARIA

Mycetismus nervosus. It has been recognized from the earliest times that the ingestion of this species of mushroom was harmful to man, and with *Amanita phalloides*, it has been included by all writers in the category of the most deadly. In common parlance *Amanita muscaria* has been called the "fly agaric" because of the household use of decoctions of the fungus as a fly poison.

The frequency with which the species has been involved in the production of human intoxication is probably attributed to its close resemblance to certain of the edible amanitas, particularly *Amanita caesarea*, which is one of the most highly regarded esculents.

In small, non-fatal doses, the effect of *Amanita muscaria* is to produce excitement, delirium, and hallucinations, and Kennan (42) has reported its common use by the peasants of Siberia to induce drunkenness. Deaths among the Koraks in the course of these drinking bouts were not uncommon. Under ordinary circumstances, however, when human cases of poisoning occur, as the result of eating this species of mushroom it is because the fungi were mistaken for some other variety and although the symptoms are violent and acute, the mortality rate is not high. Thus Gillot (10), Roch (11) and Kober (43) have reported 78 cases without a fatality, although fatal cases have been recorded by Cagliari (44), and Prentiss (45).

Symptomatology and diagnosis. The symptoms of poisoning by *Amanita muscaria* are striking and so characteristic as to present little difficulty in establishing an early and accurate

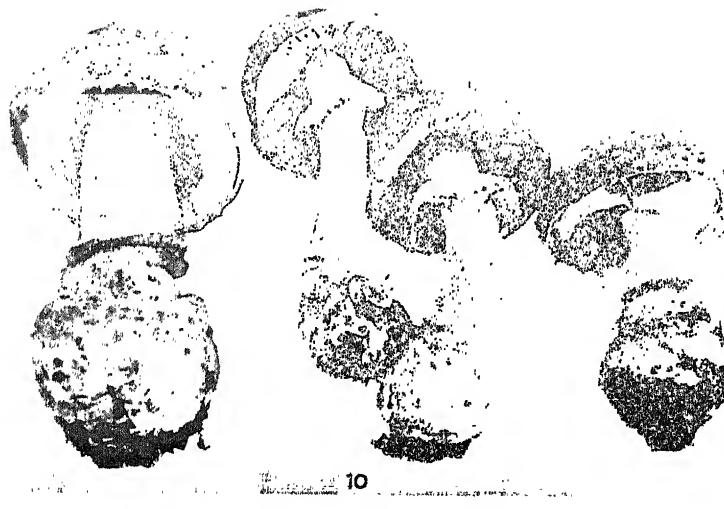


FIG. 10. *AMANITA MUSCARIA*

Various stages in the opening of the plant and formation of the veil and ring. Cap yellowish, or orange. Scales on cap and at base of stem white; stem and gills white (reduced). After Atkinson.

diagnosis. The first symptoms appear almost immediately after ingestion of the fungi, that is, within two to six hours. At first the patients exhibit an excessive salivation, profuse sweating and lacrimation, accompanied by violent retching and vomiting, together with a profuse diarrhea consisting of watery stools. The pulse is retarded and irregular, respiration is accelerated, and the patient dyspneic, the bronchi being filled with mucus. Mental symptoms come on rapidly consisting of giddiness, confusion of ideas and in some cases, hallucinations. In nearly all cases the pupils are contracted and exhibit failure to react to light and accomodation. This is important, and the condition of the pupils should always be carefully observed as they furnish great assistance in establishing a correct diagnosis.

A notable feature of cases of intoxication due to the "fly agaric" is the variation in the intensity of the different symptoms. In certain instances the gastro-intestinal disturbance is the dominating feature, while in others this is overshadowed by the cerebral and nervous reactions. When the amount of the fungus eaten is small, the symptoms are mild and may consist of a feeling of discomfort in the bowels accompanied by excessive salivation, sweating, and lacrimation. In such cases the symptoms may abate spontaneously in a few hours.

In the more severely intoxicated patients, the irritating action of the ingested fungi may be so pronounced as to lead to such a violent gastro-intestinal reaction that the alimentary canal is quickly freed of the offending material. In this event the mental and nervous symptoms then predominate. However, if a large quantity of the fungus has been eaten, the nervous and mental symptoms usually appear in the early stages of the intoxication, the patient becoming delirious, and suffering from violent convulsions, and loss of consciousness. In case consciousness is retained, death may ensue as a result of respiratory paralysis.

Finally, some cases have been observed in which an initial attack of nausea, vomiting, diarrhea, sweating and salivation,

was followed by several hours of deep sleep, from which the patients returned to consciousness profoundly prostrated but on the way to recovery.

In all uncomplicated cases of mild poisoning due to *Amanita muscaria*, and in the severe cases that are properly treated, the prognosis is good. Ultimately, such patients regain their normal health as no protracted or chronic intoxications are seen as with *Amanita phalloides*. A possible explanation of this fact may be found in the bitter taste possessed by many varieties of *Amanita muscaria* which naturally militates against the consumption of any great quantity of the fungus.

Illustrative cases. Prentiss (45) has reported two striking instances of intoxication by *Amanita muscaria*, which are perfectly characteristic and illustrate very well the sequence of events in both fatal and non-fatal cases. One of the victims, the Count de Vecchi, who was attached to the Italian Legation in Washington, purchased a quantity of mushrooms in the public market thinking them to be of an edible variety with which he was familiar in Italy. These fungi were cooked the next morning and served to the Count and his physician, Dr. K., at breakfast, and elicited commendation because of their delicious flavor. Finishing breakfast about eight-thirty, the Count experienced symptoms of acute illness within fifteen minutes, and at nine o'clock was found prostrated in his bedroom oppressed by fear of impending death. Subsequently, he became blind, developed difficulty in deglutition and became unconscious. Convulsions then supervened and were of such a violent nature as to break the bed upon which he was lying. In spite of the administration of apomorphia and atropin the Count never recovered consciousness and died the second day after the meal at which the mushrooms were eaten.

The other victim in this instance, Dr. K., physician to the Count de Vecchi, on returning to his office after breakfast, soon experienced spells of dizziness and suffered from double vision, together with other ocular symptoms. Unconsciousness quickly overcame him and he remained in this condition

continuously for a matter of five to six hours, with only one or two periods of lucidity. Under treatment with apomorphia and atropin his recovery commenced ten to twelve hours after the consumption of the fungi and his ultimate restoration to health was complete.

These cases represent very well the extremes observed in poisoning due to *Amanita muscaria*. On the one hand, there was profound depression of the nervous system resulting fatally within forty-eight hours, and on the other, rapid abatement of symptoms with no after effects.

Non-fatal cases of *Amanita muscaria* intoxication have been recorded by Boyer (46) and Sartory (47). These patients exhibited the characteristic symptoms, but all recovered.

Pathologic lesions in Amanita muscaria poisoning. Due to the few autopsies that have been performed in fatal cases of poisoning by *Amanita muscaria*, the information regarding the lesions, found in man, is very meager. However, it is said that the heart is greatly dilated and that there is an absence of the degenerative changes observed in cases of intoxication with *Amanita phalloides*.

Action of Amanita muscaria poison on animals. Some information as to the nature of the poisonous principle present in *Amanita muscaria*, and probably responsible for the intoxication of man, may be obtained by a study of the effect of extracts of the fungus upon laboratory animals. When injected subcutaneously into rabbits or guinea-pigs the action of *Amanita muscaria* has been shown by Ford and Sherrick (48) to produce the symptoms characteristic of the poisons of the muscarin-pilocarpine series. Rabbits, injected with watery extracts of the "fly agaric" exhibited pronounced salivation, conjunctival secretion, urination, diarrhea, pupillary contraction, and at first stimulated and later paralyzed respiration. In no instances were the animals fatally poisoned. Guinea-pigs were found to react quickly and violently to the extracts of *Amanita muscaria*. A few moments after the injection, conjunctival secretion, extreme salivation, diarrhea, respiratory

movements increased both in force and frequency, and finally death due to respiratory paralysis was observed.

The pupillary contractions caused by extracts of *Amanita muscaria* may be readily observed in rabbits, in a most characteristic fashion, by local application of the extract. Three or four drops of the extract instilled upon the normal conjunctiva cause the pupil of the eye to contract, the constriction lasting for a matter of three or four hours.

Finally, the effect of the extract may be tested upon the exposed heart of a pithed frog and a reaction characteristic of poisons of the muscarin-pilocarpine series observed. In this test the rate of the heart beat will be seen to diminish from 50 to 60 per minute to 5 or 6 per minute but normal activity will be resumed upon the application of a solution of atropin. In another experiment, Ford and Sherrick showed that introduction of four drops of extract of fungus into the ventral lymph sac of a frog produced, within ten minutes, a diminution in the heart rate to 5 or 6 beats per minute, and complete stoppage within twenty minutes. The application of atropin solution even an hour later brought the heart action back to normal in less than fifteen minutes, and it has been shown by many investigators that this prolonged pause is characteristic of muscarin. On the other hand, Harnack and Meyer (49) have shown that pilocarpine produces but a temporary cessation of the heart's activity. It is thus indicated that *Amanita muscaria* owes its activity to its content of muscarin or pilocarpine the probabilities favoring muscarin.

The toxic principle of Amanita muscaria. Schmiedeberg and Koppe (50) first isolated the toxic principle from *Amanita muscaria*, in 1869, and called it *muskarin*. In their process the fungi were extracted with alcohol and impurities removed by precipitation with lead acetate. The filtrate was then freed from alcohol, taken up in water, and shaken with animal charcoal. At this point the suspension is rendered slightly acid and precipitated by the addition of mercury-potassium-iodid, preferably a concentrated solution containing an excess of

mercuric iodid. The precipitate, which is thus obtained, is then dried between filter papers under pressure and then decomposed by adding hydrochloric acid. The resulting compound, muscarin-hydrochlorid is then dried over sulphuric acid and yields crystals having the form of needles and prisms. Harnack (51) believed that the crystals of muscarin-hydrochlorid, thus obtained, contained, in addition to the physiologically active muskarin, an inactive base which he called *amanitin* which is probably cholin or bilineurin. Separation of the two substances is easily effected by fractional filtration because of the ease with which the muscarin salt goes into solution.

A more recent method of extracting the active principle from *Amanita muscaria*, and perhaps one to be preferred to that of Schmiedeberg and Koppe, has been worked out by Harmsen (52). In this process 100 grams of chopped fungi are extracted for several weeks with 96 per cent alcohol, the alcohol is then filtered off and the extract reduced to the consistency of a syrup, over the water bath. The brownish-black material thus obtained is then repeatedly treated with alcohol, evaporated, and finally mixed with sand and desiccated. When dry, the mixture is treated with absolute alcohol, evaporated on a water-bath, taken up in water and heated until all the alcohol has been driven off. At this point a slight precipitate forms, and the fluid is filtered through a Berkefeld filter. The clear yellow neutral fluid thus obtained is then taken up in such an amount of water as will cause one cubic centimeter of the solution to correspond with one gram of the fungi. In this state the active principle is in combination with an atropin-like base (pilz-atropin) from which it is freed by making it weakly alkaline with sodium carbonate and repeated shaking with ether. It is then neutralized with dilute hydrochloric acid, the ether is removed by evaporation, and the material is ready to be used in experimental tests.

Chemical nature of the toxic principle in Amanita muscaria. As previously mentioned Schmiedeberg and Koppe (50) were the first to isolate from an extract of the "fly agaric" a syrupy

base having powerful physiological properties, arresting the frog's heart in diastole and being antagonized in its action by atropin. Somewhat later, Harnack (51) obtained choline aurichloride and muscarin aurichloride by fractionation of extracts of the fungus. From cholin Harnack and Schmiedeberg (53) subsequently obtained a substance which was called "synthetic muscarin" and which exhibited all the physiological properties and analytical values of muscarin from *Amanita muscaria*. Nothnagel (54) corroborated the formation of "synthetic muscarin."

From the pharmacological side Boehm (55) showed that the "synthetic muscarin" of Schmiedeberg and Koppe was far weaker than natural muscarin, and that it had a curare type of action on the atropinised frog, not shown by natural muscarin. Meyer, using Nothnagel's preparation confirmed these observations. Ewins (56), later showed very clearly that the "synthetic muscarin" obtained by Schmiedeberg and Koppe, and by Nothnagel, was identical with choline nitrous ester, while Dale (57) showed this ester to exhibit the same physiological properties as those attributed to "synthetic muscarin."

Harnack (51) and Nothnagel (54) are the only investigators who claim to have isolated natural muscarin from *Amanita muscaria* in a pure state. Confirmation of this work is lacking. Most recently King (58) has sought to extract natural muscarin from the fungus, and succeeded in obtaining muscarin chloride, which, when tested on an isolated loop of the rabbit's intestine produced slightly sub-maximal contraction at a dilution of 1 part in 67 million parts of water. A dilution of 1 in 600 millions produced an appreciable effect.

Physiological action of the poisonous principle. Although muscarin is present in the fungus in relatively small amount it is extremely active as indicated by the observations of King cited above. In the animal body its action is directly upon the autonomic or sympathetic nervous system, producing increased secretion from the various glands of the body by stimulating the terminal filaments of the secretory nerves, and

paralysis of the heart and respiration by a corresponding stimulation of the inhibitory endings of the vagus nerve.

In experimental tests of solutions suspected of containing muscarin, application to the exposed heart of a pithed frog will result in immediate stoppage in diastole if muscarin is present. This action is quickly overcome by the application of a dilute solution of atropin, but after resumption of normal contraction and dilation, further application of muscarin has no effect.

Schmiedeberg (59) isolated from the Siberian *Amanita muscaria* a second principle, having much the same action as atropin, producing dilatation of the pupils, which he called *muscaridin*. It is the presence of this substance in *Amanita muscaria* which seems to explain the relative immunity of the Koraks to fatal poisoning by the fungus. Kober (60) has since given the name "Pilz-atropin" to the muscaridin of Schmiedeberg. Finally, Harmsen (52) has shown that there is apparently another poison in *Amanita muscaria* which causes long-continued convulsions and is not offset by atropin. He called this *Pilz Toxin*. The relation of this substance to fatal cases of *Amanita muscaria* intoxication needs further investigation.

III. MICELLANEOUS MUSHROOM INTOXICATIONS

Mycetismus gastro-intestinalis. Poisoning of this type is quite common and, although the patient may be violently ill, fatalities seldom occur. As the name indicates the symptoms are predominantly gastro-intestinal. However, they are distinctly transient. Usually there is a period of 2 to 4 hours after the fungi are eaten before any discomfort is felt, but in some cases onset is almost immediate.

In those cases attributable to the ingestion of the large *Boletus satanas*, which measures 5 to 8 inches in diameter, or *Boletus miniato-olivaceus*, the symptoms consist of nausea, vomiting, diarrhea, chilly sensations, prostration, and limitation of the field of vision. As a rule such cases yield readily to treatment or recovery is spontaneous in a day or two.

Rapidity of onset characterizes poisonings due to the large *Entoloma sinuatum* and *Entoloma lividum*. The initial symptoms are usually violent, consisting of vomiting, diarrhea, syncope, periods of remission, pupillary changes, excessive thirst, dryness of the mouth, difficulty of speech, unimpaired mental reactions, but recovery is rapid.

Finally, there are cases of poisoning due to *Lepiota morgani* and *Russula emetica* in which discomfort is felt almost at once after the fungi are eaten. Violent vomiting followed by profuse, painless, watery stools characterize these cases.

Mycetismus sanguinareus. In these cases the most notable features are the rapid development of jaundice and anemia, accompanied by a coffee-brown urine due to a true hemoglobinuria. *Helvella esculenta* is the only species known to give rise to this type of poisoning and acts by virtue of the presence in it of a resistant hemolytic poison which was called by Boehm and Külz (61) *Helvetic acid*. In common parlance, *Helvella esculenta* is known as the false morel or lorchel.

Mycetismus cerebralis. Transient excitement and hallucinations, the patients exhibiting a peculiar condition of hilarity and a degree of mental confusion, characterize these cases. Usually there is no gastro-intestinal disturbance and the severity of the symptoms varies greatly. Onset is almost immediate after the fungi are eaten and the patient exhibits cardiac and respiratory depression, dilated pupils that fail to react to light and accommodation, numbness and tingling in the lower limbs, prostration, and drawn facial expression. Recovery is the rule in poisoning of this type, which is attributed solely to two species of *Panaeolus*.

IV. TREATMENT OF MUSHROOM POISONING

The descriptions already given of the outstanding symptoms generally seen in the different types of mushroom poisoning, should enable the physician to establish a diagnosis. However, in all cases of mushroom intoxication an attempt should be made to discover, if possible, and at the earliest moment, the

particular poisonous fungus, that has been eaten, as to a certain extent the treatment and prognosis depend upon the species that has been ingested. Consequently, every effort to elicit accurate descriptions of the fungi eaten should be exercised, as very often this information from the patient alone, will be sufficient to enable recognition of the variety. At any rate, bits of the fungi, either from left-over scraps or from the vomitus or stools should be obtained and submitted to a mycologist for identification. However, the severity of many cases will require vigorous and prompt treatment and identification of the fungus ingested will perforce be deferred.

In all cases of mushroom intoxication complete elimination of any of the offending material that may be in the stomach or intestines should be assured. To accomplish this end gastric lavage and high enemata should be given and continued until no more solid material appears in the wash fluid. These measures should be carried out in spite of the prominence of the gastro-intestinal symptoms in the case as the natural vomiting and purging may not be sufficient to free the intestinal tract of all the fungus.

The injection of atropin, either subcutaneously or intravenously, depending on the severity of the poisoning, seems also to be indicated in all instances. This drug is of especial value in intoxications with the muscaria but its injection can do no harm in any case so it may be given before the exact diagnosis is established.

Because of the relatively greater frequency and importance of poisoning by *Amanita phalloides* and *Amanita muscaria* the treatment of these cases may be considered separately and in some detail.

Amanita phalloides poisoning. In poisoning due to *Amanita phalloides* the prognosis is doubtful and little can be done except to apply the general measures recommended above. The intense pain may be somewhat relieved by the administration of opiates and stimulants such as strychnine may be given in periods of collapse. Digitalis should be used if the heart

function is impaired. Any measures applicable to nephritis may be employed to offset the damage to the kidneys, which is a regular feature of these cases. Maheu (62) has recommended the administration of charcoal by mouth in order to adsorb the poison.

Lacey (63) obtained good results in the treatment of 18 cases by gastric lavage, using salt solution, followed by thoroughly washing out the stomach with at least a quart of potassium permanganate solution, made by diluting a strong stock solution until it was a deep pink color. This procedure was repeated several times daily and after each gastric lavage two or three ounces of saturated solution of magnesium sulphate was left in the stomach. All of the patients thus treated were prostrated when admitted to the hospital, were very weak, had low blood pressure and subnormal temperatures and much albumin with many casts and some blood-cells in their urine. They were given a light nephritic diet and plenty of water to drink, and between treatments a Murphy drip, consisting of a sodium bicarbonate solution, was left going as long as retention was possible. Under this treatment all but one of the victims eventually recovered.

Amanita muscaria poisoning. As the symptoms in *Amanita muscaria* poisoning are due to the action of muscarin on the nerve endings, a perfect physiological antidote is available in atropin. However, vomiting and purging are to be encouraged as aids in freeing the digestive tract of all the offending material. Atropin should be given at once and repeatedly, either subcutaneously or intravenously as indicated, as well as stimulants such as strychnin, digitalis, strophantus, and alcohol. At the same time the treatment employed by Lacey, described above under poisoning by *Amanita phalloides*, should prove of value in this type of poisoning as well.

The prognosis is excellent in these cases provided the patient is carried over the period of acute muscarin-poisoning as there are no lesions in the internal organs.

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CHAPTER IX

GRAIN INTOXICATIONS

I. Ergotism. Historical. Etiology. Clinical symptoms and diagnosis. Active principle in ergot. Extraction of the active principle. Pharmacologic action of the principle. *II. Lathyrism.* Historical. Etiology. Symptomatology and diagnosis. The active principle in lathyrism. Pathology. Prophylaxis.

I. ERGOTISM

Historical

Although virtually unknown in America, the grain intoxications have been the cause of severe epidemics in other countries. Of these intoxications, ergotism and lathyrism are the most important. In those localities where ergotism has occurred in epidemic form, it has frequently been known as "Saint Anthony's Fire."

The first epidemic of certain identity ascribed to ergot is recorded in the annals of the convent of Xanten on the Rhine (1), although there are vague references to a grievous disease simulating ergotism in the Old Testament, as well as in the writings of Hippocrates and the Arabians. A hundred years after the epidemic referred to above, that is, during the tenth century, the city of Paris was so sorely afflicted with ergotism that the people flocked to the churches to pray for deliverance from the disease. During the same century somewhat over 40,000 deaths were attributed to this disease in the regions of Limousin and Aquitaine. However, destructive as it had been, the scourge was most virulent toward the end of the eleventh and during the first half of the twelfth century, at the time of the Crusades. During these years, Germany, Flanders, Burgundy, Denmark and England suffered heavily, whole districts being depopu-

lated as if by plague. During the succeeding centuries the evil was most destructive in times of bad harvest and famine, but slowly science did for these miserable people what the saints failed to do, and Thuillier discovered that the cause of the plague lay in the spurred rye; that the severity of the disease is in proportion to the dose of this poison; and that the rye is spurred only in damp and cold seasons. This better knowledge of the causes of the disease somewhat lightened the weight of the plague, although it did not cease to exist in epidemic form. During the last century severe epidemics were observed in East Prussia in 1867-68 and in Nanterre, France, in 1894, while in 1907-08 an epidemic was reported in Hungary. At the present time the disease is practically confined to Russia, in many parts of which it is apparently endemic.

Etiology

Ergotism results from the consumption of rye, wheat, oats, or other grain which is infected with a vegetable parasite, a fungus, known as *Claviceps purpurea*. This fungus produces a mycelium of long, spindle-shaped corrugated bodies that are deep violet in color and that replace the grain in the head of the rye or wheat. Those grains not displaced become brownish or purple in color and when milled produce a correspondingly discolored flour having a sour odor. The existence of this condition in the grain is easily detected by microscopic examination, while in flour it may be determined by the method of Böttger: the sample is mixed with ether and a few crystals of oxalic acid are added, it is then brought to a boil and allowed to become clear by standing. If the clear supernatant fluid shows a red tinge, ergot is present.

Clinical symptoms and diagnosis

The symptoms attending poisoning from the use of grain infected with *Claviceps purpurea* are extremely varied. In the acute form, which is more commonly observed in children, there

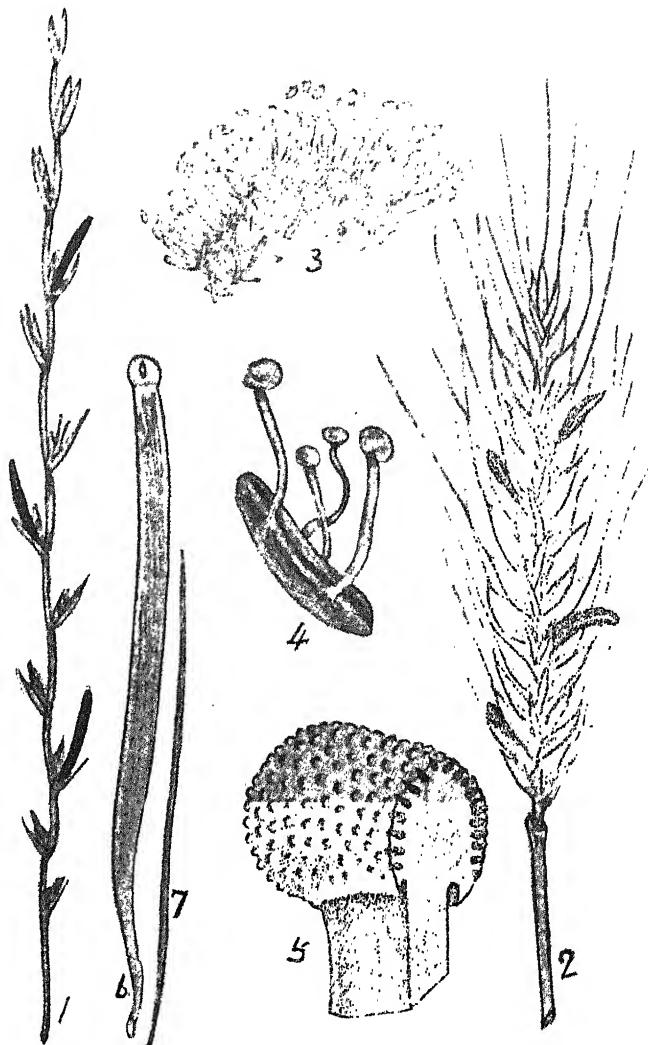


FIG. 11. *CLAVICEPS PURPUREA*

(1), ergot on rye grass; (2), ergot on rye; (3), section of a portion of the conidial form of fruit, $\times 300$; (4), a sclerotium or ergot; (5), head of ascigerous form of fruit; (6), an ascus, $\times 300$; (7), a single spore, $\times 300$; After Jordan.

are heaviness of the head, giddiness, depression of the spirits, and formication, which may pass rapidly into colic, tympanites, clonic and tonic cramps, precordial anguish, violent vomiting, purging and stupor. In general there are two distinct types of intoxication that are spoken of as acute *spasmodic* or *convulsive ergotism* and chronic or *gangrenous ergotism*. In most epidemics one or the other type of intoxication alone is seen, although epidemics have been reported in which both types were observed. When convalescence follows an acute attack, which is rare, it is tedious and imperfect, with frequent relapses and sequelae of epilepsy, weakmindedness and cataract. In fatal cases, death is apparently caused by exhaustion.

Ergotismus spasmoticus or *convulsivus*. This type of intoxication is inaugurated by a feeling of numbness in the fingers and hands which progresses to include the whole body. The reports of many observers, notably Meyer and Gottlieb (2), agree that very shortly afterwards gastro-intestinal symptoms set in, the patient repeatedly vomiting and at the same time developing a severe diarrhea. Severe muscular contractions become evident at this stage, the flexors of the arms and legs being especially subject to very painful tonic contractions. Following this, epileptiform convulsions appear, lasting perhaps for several hours and being exceedingly painful. Finally the nervous system becomes involved and a degree of imbecility develops.

Ergotismus gangrenosus. The onset of this type of poisoning is much the same as in *Ergotismus convulsivus*, with progressive numbness beginning in the extremities, vomiting and diarrhea. In the course of a few days dry gangrene sets in, the parts most affected being the fingers, toes, lobes of the ears and the soft portion of the nose. At this stage the progress of the gangrene is characterized by agonizing pain, which "penetrates the affected limb or limbs like fire." Later there is complete anesthesia. The affected portions lose their color, becoming livid, but shortly appear darkened or black. As a rule the gangrene is dry but moist gangrene is seen occasionally. An area of

inflammation marks off the dead portion, the epidermis parts from the underlying tissues and there is eventually more or less loss of tissue which separates without haemorrhage.

In the case of pregnant women intoxication of either type frequently leads to premature births and abortions are common. It was the recognition of this action of ergot that led to its frequent and unlawful use as an oxytocic.

Active principle of ergot

In the unrefined state ergot acts in one of three ways, namely, in the excitation of spasms (convulsive ergotism), in the causation of gangrene (gangrenous ergotism), and finally upon the uterus.

The first careful study of ergot was made by Wiggers (3) who described among other things an alcohol-soluble resin extracted from the infected grain which he called *ergotin*. This substance, which was insoluble in water or ether, possessed all the toxic properties of ergot. The first proof of the presence of fixed alkaloids in ergot was presented by Wenzell (4) however, when he obtained two impure resinous preparations giving alkaloidal reactions, which he called *ecboline* and *ergotine*. Somewhat later the first well defined crystalline alkaloid from ergot was obtained by Tanret (5), who gave it the name of *ergotinine* to distinguish it from the resinous ergotine of Wenzell. Tanret's crystalline alkaloid has been found by all subsequent workers, but according to Kobert (6) this substance has but slight if any physiological activity. From the mother liquor of this base Tanret obtained a further alkaloid in amorphous form which he called *amorphous ergotinine*. This substance has since been obtained by Barger and Carr (7) in crystalline form and is called by them *ergotoxine* and is now regarded as a chemical entity. It has been shown by these investigators to possess great physiological potency and a close relationship between ergotoxine and ergotinine is indicated by the fact that the former may be converted into the latter by boiling with acetic anhydride. According to

Dale (8) ergotoxine produces not only the characteristic reactions of ergot, but also gangrene of the cock's comb and other ergot effects as described by Kober. Crystalline ergotinine uncontaminated with ergotoxine does not produce these effects at all, or at least only to a slight extent.

Extraction of the principles

Ergotinine. This substance is extracted by ether and the ether then evaporated. The resulting oil is then mixed with light petroleum from which the alkaloid is precipitated. In this state it is unmixed with resin and when taken up in alcohol it yields long white crystalline needles having their sides not quite parallel and with symmetrical ends. It gives the characteristic color reactions as described by Tanret, that is, on the addition of concentrated sulphuric acid to the solution in ether or ethyl acetate, a transitory orange appears which soon changes to blue.

Ergotoxine. The extraction of this substance is a continuation of the process by which ergotinine is obtained. The caustic liquor from which ergotinine has been extracted is first neutralized and made alkaline with sodium carbonate and then extracted with ether. The residue is dissolved in 80 per cent alcohol and a slight excess of phosphoric acid in alcohol is added. In a few hours the ergotoxine phosphate crystallises out and may be recrystallised from alcohol. In its purest form it is a light white powder.

Barger and Dale (9) have found watery extracts of ergot possessed considerable physiological activity, even after being freed of ergotoxine. From these extracts they obtained para-hydroxyphenylethylamine and a trace of iso-amylamine which are derived from the amino-acids, tyrosine and leucine, respectively. Whether these substances are produced by the ferments of the fungus or by bacterial action during the non-sterile process of extraction, is still an open question. More recently Spiro and Stoll (10) have obtained a crystalline base having all the physiologic activity of ergot, which they call

ergotamin. It may eventually be shown that ergotamin is really the active principle, while amorphous ergotoxine is simply a decomposition product of this substance.

Pharmacologic action of the principle

The sensory nerves are paralysed but it is uncertain whether the action be central or peripheral, according to Brunton (11). The muscles and motor nerves are unaffected. The arteries are thrown into a state of contraction, producing a rise in blood-pressure. In some measure, however, this rise is due to stimulation of the vasomotor centre in the bulb, although the main action is on sympathetic nerve cells. None of the action is peripheral on the vessels. In the constricted arterioles a glutinous matter made up of blood corpuscles and serum forms a thrombus and the walls of the vessels undergo a hyaline degeneration, especially of the tunica intima. After death the abdominal viscera are found "inflamed" (Brunton) and the lungs are always congested. The uterus, intestines and bladder are tetanically contracted.

II. LATHYRISM

Historical

Centuries ago the observation was made that the habitual use of certain peas as food was liable to lead to paralysis. Thus in the writings of Hippocrates (12) it is recorded that, "at Ainois, all, men and women, who ate continuously peas, became impotent in the legs, and that state persisted." In this instance, it is impossible to identify the exact pulse referred to. But later writers allude specifically to the peas of three species of *Lathyrus* extensively used as food for man and domestic animals which exerted a poisonous effect when included in the dietary for any considerable length of time.

The earliest mention of poisonous species by name is in an edict of the Duke of Würtemberg (13) in 1671, who forbade the use of flour made from peas for bread making as it caused

an incurable paralysis of the legs. From time to time, similar warnings were issued from other sources. In 1786 the Florentine Government issued a warning against the use of the species *Lathyrus sativus*, and in 1820 and 1822 the veterinary school at Alfort (Paris) warned against the use of *Lathyrus cicera*. However, it was not until the nineteenth century that reports of extensive outbreaks of poisoning among men and domestic animals, due to continued consumption of certain species of *Lathyrus*, began to appear with unusual frequency. Such outbreaks have occurred in Europe, particularly in France and Italy; in Northern Africa, chiefly in Algeria; and especially in India. As examples of extensive epidemics in these regions those reported by Ramazzini (14) in the Grand Duchy of Modena; by Desparanches (15) in the Department of Loire et Cher; by Proust (16) in Algeria; and by Sleeman (17), Irving (18) and Buchanan (19) may be cited.

Probably the best reviews of this disease in which every aspect of the question—historical, social, economic, clinical, botanical, chemical, and experimental—is treated are those of Schuchardt (20) Buchanan (19), Stockman (21) and Anderson, Howard and Simonsen (22).

The disease was given the name *Lathyrism* by Cantani (23) in 1873.

Etiology

Epidemic and endemic poisoning in man and domestic animals has been traced to at least three species of *Lathyrus*, namely *Lathyrus sativus*, *Lathyrus cicera*, and *Lathyrus clymenum*. Of these *Lathyrus sativus* is principally grown in India, *Lathyrus cicera* chiefly in France, Italy and Algeria; and *Lathyrus clymenum* in Algeria, the Levant, Northern Africa, and Spain.

In Hindustani the seeds of *Lathyrus sativus*—the supposed cause of poisoning in man—are known in the vernacular as *khesari*. In Bengal they are known as *teora*, while in Sind, the Punjab, and the North-West Provinces, they are called *mattar*.

Where grown, khesari furnishes a considerable portion of the proteid in the dietary of the poorer classes at all times, but in times of food shortage it forms the chief constituent of the dietary for months at a time. It is used chiefly as flour in bread, as porridge, or as a dal—a general term for all kinds of split peas—the peas being cooked with oil or boiled in water.

In those areas where khesari is eaten regularly or in excessive amounts for any time lathyrism is encountered. This disease is endemic in some areas, and rapidly becomes epidemic as famine conditions are approached and the proportion of khesari to the total food intake increases. Nearly all investigators have emphasized the apparent association between the disease and long-continued use of the seed of *Lathyrus sativus* and there seems little reason to doubt the close connection of the two.

The theory most generally offered, heretofore, in explanation of the association between lathyrism and consumption of the seeds of *Lathyrus* is that the disease is due to the presence of an alkaloid. Consequently the chemistry of the seeds has been investigated by numerous workers, but without concordant results. Stockman (21) and Dilling (24) obtained substances of an alkaloidal nature from the peas with which they were able to produce symptoms when inoculated into animals. Acton and Chopra (25) extracted a water-soluble amine which they considered would account for the syndrome of lathyrism and with which they obtained pharmacological effects by inoculation into animals. On the contrary, Guillaume (26) was unable to demonstrate any poisonous bases in the seeds of various species of *Lathyrus* which he examined.

In this connection it is to be pointed out that in none of this work was the investigation carried out on botanically pure seeds of *Lathyrus sativus*. The importance of this fact becomes clear when it is realized that other almost indistinguishable legumes commonly grow in the fields with this species and that a mixture of seeds therefore results. Thus it may be that suspicion has been cast upon *Lathyrus sativus* entirely, unjustly,

and, in fact, recent investigation indicates that such is the case, as Howard, Simonsen, and Anderson (27) found the botanically pure seeds of *Lathyrus sativus* free from any trace of alkaloid. They did find, however, a base or mixture of bases giving alkaloidal tests, in the grain of a weed known as *Vicia sativa*, var. *angustifolia*, or "akta", which grows with the *Lathyrus*. Still more recently Anderson, Howard and Simonsen (22), pursuing this investigation further, have confirmed the absence of any alkaloidal substances in the botanically pure seed of *Lathyrus sativus*, and have found in feeding experiments that "the animals thrived on a diet largely composed of this grain, and actually increased in weight and improved in general condition." On the other hand, examination of the seeds of the weed *Vicia sativa* var. *angustifolia*, commonly called akta, which grows with *Lathyrus*, revealed the fact that they contained bases with alkaloidal properties. Two bases, vicine and divicine, and a cyanogenetic glucoside, vicianin, were isolated in a pure state and used in experiments upon animals. When injected into guinea-pigs, divicine, which occurs in akta in combination with a sugar as the glucoside vicine, produces a characteristic and fatal disease. When fed to ducks akta causes death. In monkeys it gives rise to symptoms attributable to its effect upon the nervous and muscular systems. As to its relation to cases of human lathyrism these investigators say "we are not yet in a position to state in the absence of pathological proof, that akta is the cause of lathyrism in man."

Symptomatology and diagnosis

A notable feature of the disease is that only the poorest classes of the people are affected and that among these the proportion of men and women is about ten to one. To explain this incidence Stockman (21) says two hypotheses have been advanced, the one, that men are habitually heavier eaters than women, the other, that men are more exposed to cold and wet and fatigue, conditions which seem to enhance the action of the poison.

The symptoms become manifest only after eating quantities of the peas for about two months, when cramps develop in the calves of the legs, which feel weak and trembly and are accompanied by considerable pain in the lumbar regions. Both legs are affected at the same time, first in the calves and then in the thighs, progression becoming difficult. There is no wasting, no loss of muscular tone, no true tremors, and sensation is quite unaffected. Often a peculiar rigidity of the dorsolumbar muscles is set up on the side opposite to each leg as it is advanced in turn so that the trunk is thrown backwards and sideways against the weight of the advancing leg. As the leg is thrust forward the toe is pointed and the heel drawn up so that the ball of the foot comes in contact with the ground before the heel, which may never touch. In this case the gait becomes a characteristic weaving roll. The skin reflexes may or may not be affected, while the tendon reflexes, both the knee jerk and the ankle clonus, are exaggerated. In some cases, control of the sphincters of the bladder and rectum is temporarily lost. The arms, trunk, head and neck muscles are unaffected, the mind remains clear, speech is natural and the eyes are normal, reacting to light and accommodation.

The active principle in lathyrism

Many attempts have been made to isolate the poisonous principle from *Lathyrus*. Bourlier (28) for example, obtained an alcohol and ether extract which caused symptoms of motor paralysis of frogs, tortoises and sparrows. Marie (29) isolated an alkaloid which, however, was physiologically impotent. Astier (30) obtained a volatile alkaloid which he called *lathyrin* but which was never tested on animals. With an alcohol extract, however, he was able to produce tremors and finally paralysis or paresis of the hind legs in dogs when it was injected subcutaneously. More recently Stockman (21) has been able to isolate from the seeds of *Lathyrus sativus* a toxic alkaloid which produced paralysis in frogs and mammals. Subsequently Dilling (24) obtained two alkaloids from Group II and Group

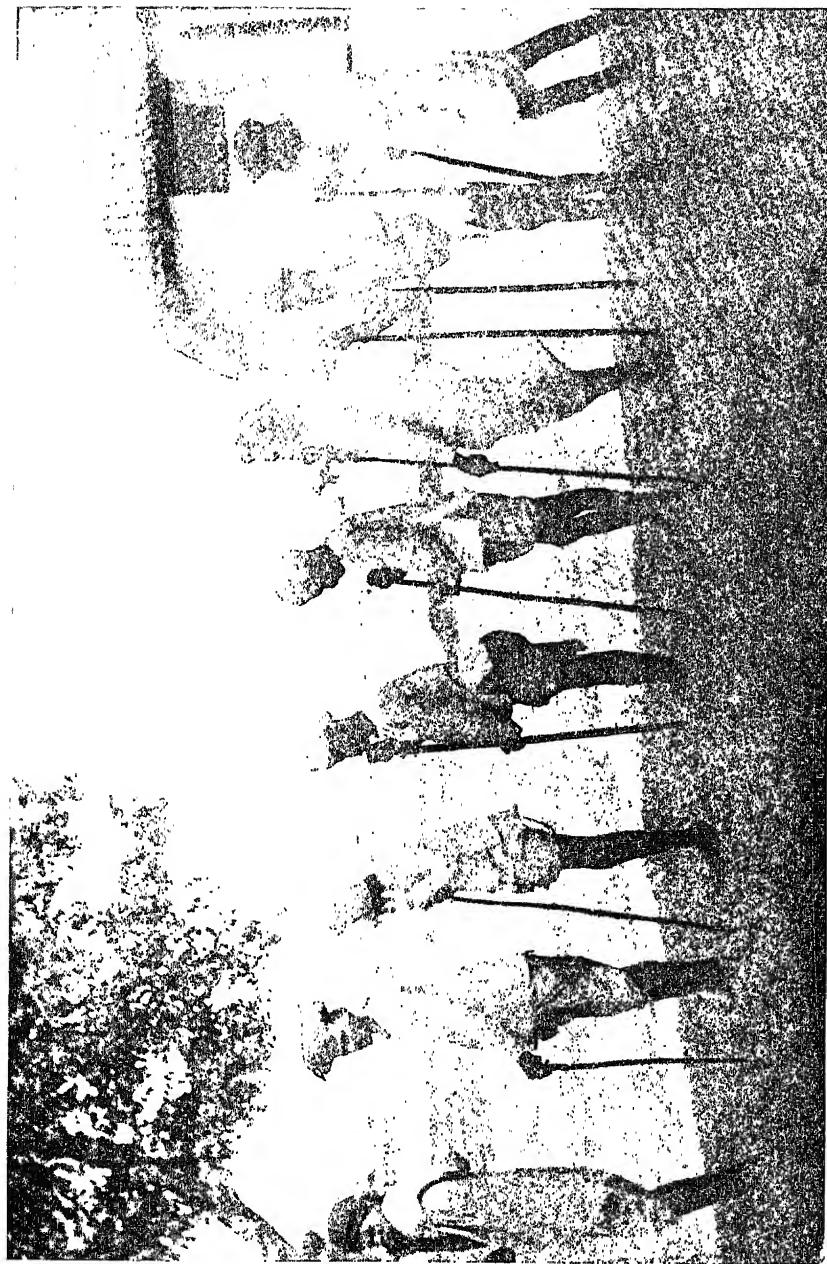


FIG. 12. HUMAN CASES OF LATHYRISM

1 and 2, able to walk with one stick in one hand; 3, 4, 5, 6, able to walk with a long stick held by both hands; 7 and 8, able to walk with a long stick held in each hand. After Stockman.

IV by the Stas-Otto process of fractionation which were characterised by the production of paresis and by first increasing and then diminishing the reflex action in frogs. Finally Howard, Simonsen and Anderson (27) in an attempt to determine the cause of the disease, as mentioned above, have reported the grain of *Lathyrus sativus* as free from any trace of alkaloid, but have revealed a base, or mixture of bases, responding to alkaloidal tests, in the grain of a weed *Vicia sativa*, var. *angustifolia* which grows with the *Lathyrus*. In these seeds, Ritthausen (31) years ago noted the presence of a base to which he gave the name *vicine* while Bertrand (32) and his co-workers isolated from *Vicia sativa* a cyanogenetic glucoside, *vicianin*, which was closely related to amygdalin. Howard originally expressed the belief that vicine or its hydrolytic product divicine might be the physiologically active principle in the disease as Dox and Yoder (33) have shown that closely related bodies possess markedly poisonous properties. More recently Anderson, Howard and Simonsen (22) have confirmed the belief that vicine is itself non-toxic, and have shown that its hydrolytic product, divicine, is highly poisonous and produces serious derangement of the nervous system.

In the small number of experiments with extracts of *Lathyrus sativus*, using lower animals, it may be repeated that Stockman observed paralysis of the peripheral nerves in monkeys and other symptoms referable to an action on the central nervous system. Somewhat later Dilling reported on the effects of his extractions as follows: the alkaloid from Group II of the Stas-Otto process of fractionation first produced in frogs paresis, due to action on the central nervous system, increase and then diminution of the reflex activity of the cord, and finally paralysis of the voluntary peripheral nerve endings, followed by diminution and loss of the excitability of the voluntary muscular tissue. The alkaloid from Group IV has the same action on the central nervous system and the reflex mechanism of the cord, but has a predominant action on the spinal cord, where it apparently interferes with the receptive side

of the reflex arc. It seems to have no effect on the voluntary nerve endings but lowers the direct excitability of the muscle tissue and has an action on the relaxation period similar to veratrine.

As yet no report has been made by Anderson, Howard, and Simonsen regarding the pathological lesions produced in their experimental animals when confined to a diet containing the pure seeds of akta.

Pathology

Buchanan describes the symptoms as corresponding exactly with those of Erb's spastic paraplegia and as due to degeneration of the crossed pyramidal tracts in the cord. Irving, Hendley and Kirk describe it as a form of paraplegia brought on by exposure to cold and wet, in persons predisposed by a *lathyrus* diet. Proust believes that the symptoms correspond to a transverse myelitis, followed by degeneration of the lateral and posterior columns. And finally Cantani has stated the belief that the difficulty lay in the muscles as he found some fatty degeneration of the fibres in the flexors of the leg.

Prophylaxis

As a result of the investigations of Anderson, Howard, and Simonsen it appears that *Lathyrus sativus* is itself harmless and that the danger to man lies in its cultivation with *Vicia sativa* var. *angustifolia* present as a weed. In order to remove this source of danger for man the cultivation of khesari in pure culture is obviously indicated and this may be readily accomplished by weeding out the akta while the plants are young and easily distinguishable. In this way the crop produced will be practically pure khesari and the seeds may be consumed without danger of contracting *Lathyrism*.

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CHAPTER X

MILKSICKNESS

Historical. Etiology. Symptomatology. Diagnosis. The Poisonous Principle. Pathology. Treatment.

HISTORICAL

In North Carolina milksickness undoubtedly occurred as early as 1778 and it was frequently reported in Tennessee, Kentucky, Ohio, Indiana, Michigan, and Illinois, during the early pioneer days. In different localities the disease has been known by a variety of names such as trembles, slows or sloes, colica trementia, milk sick, staggers, milk fever, puking fever, alkali, or paralysis intestinalis.

In the earlier years of the last century the disease was quite common, and a voluminous literature on the subject has accumulated, although only of recent years has any reliable information as to its etiology been obtained. Since about 1840 the number of cases seen each year by clinicians has gradually but steadily fallen off, although even now outbreaks of milksickness occur from year to year, especially in the more sparsely populated areas of the Southern and Mid-Western States.

One of the first professional accounts of the disease was that by Drake (1), and after him accounts of similar outbreaks were recorded by numerous authors. Of recent years epidemics have been reported by Jordan and Harris (2) (3) (4) in New Mexico and Illinois; by Walsh (5) in Illinois in 1908; by Clay (6) in Illinois in 1913; by Schwarze (7) in Illinois in 1917; by Graham and Boughton (8) in Illinois in 1923; and by Wilkinson (9) in North Carolina in 1925.

Excellent historical accounts of the disease have been reported by Graff (10), McCoy (11), Jordan and Harris (3), and Sackett (12) and for greater detail the reader should consult these works.

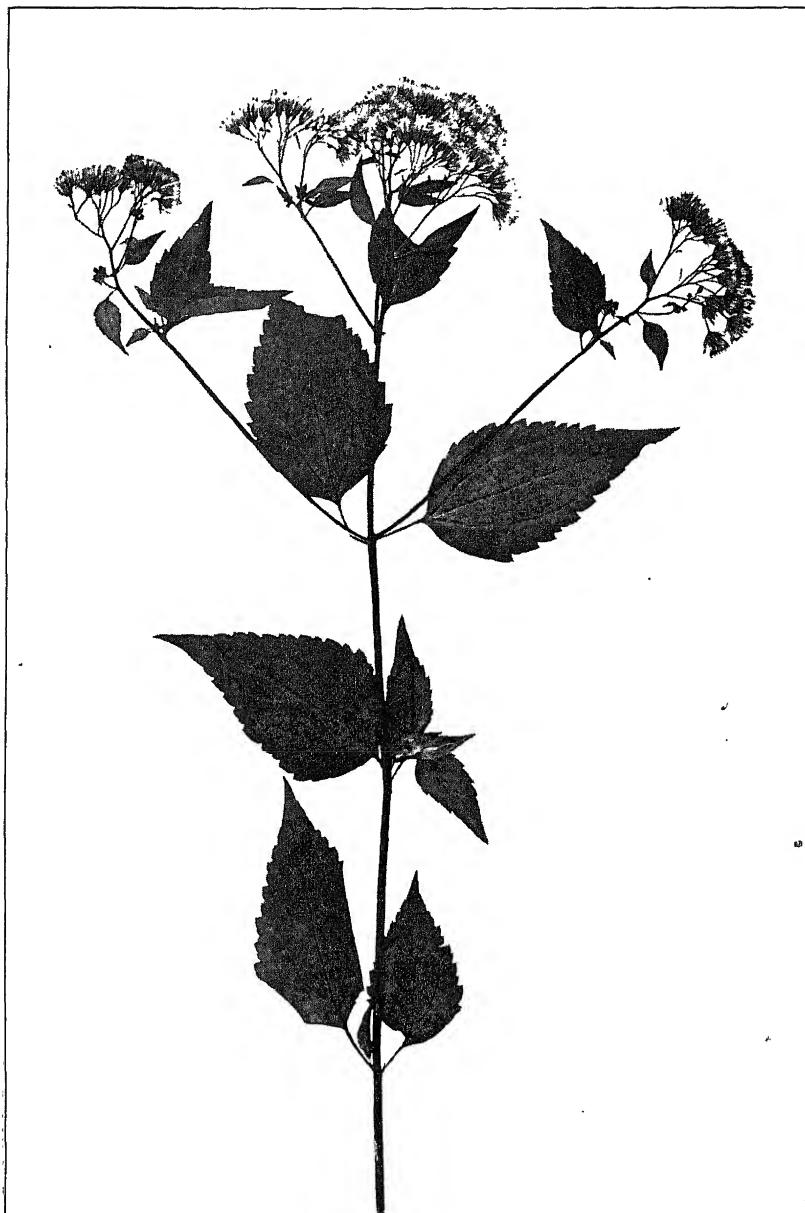
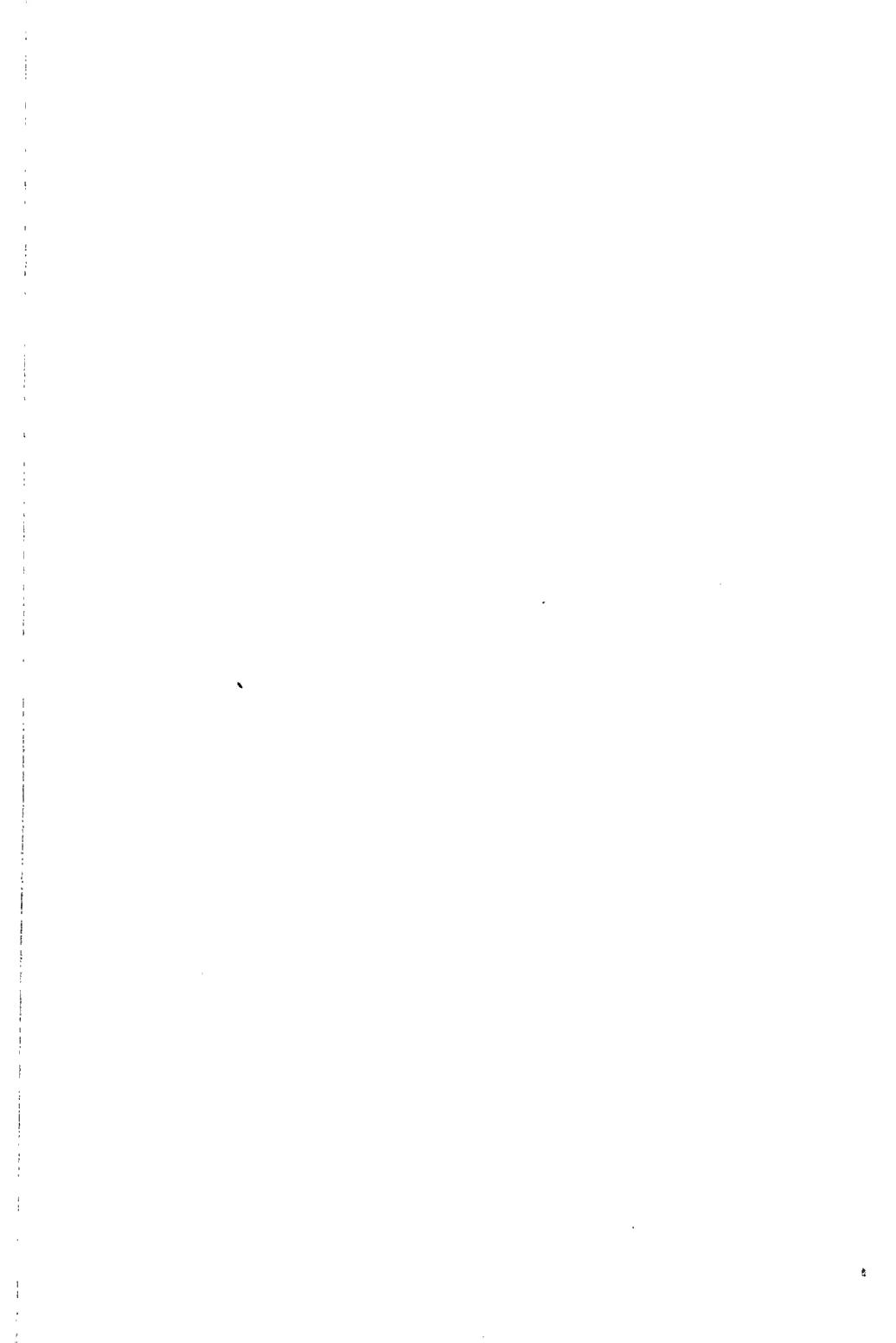


FIG. 13. *EUPATORIUM URTICAEFOLIUM* OR WHITE SNAKEROOT, SHOWING THE CHARACTER OF THE LEAVES AND FLOWERS. AFTER CURTIS



ETIOLOGY

Milksickness in man and trembles in cattle seem to have followed much the same course, and this fact tends to indicate a common origin, or at least an intimate relation, of causal agents. In the earlier days, long before anything was known as to the etiology of milksickness, the development of the disease in man was observed to always parallel the outbreak of trembles in cattle, and it was not uncommon for whole communities to be forced to migrate in order to escape the sickness. Somewhat later, when the occurrence of the disease became associated with pasturage of cattle on particular uncleared lands, certain wild pastures and swampy lowlands, it came to be common practice to fence off these areas. This was done in White County, Tennessee, where "Milksick Mountain" was surrounded by a fence between seven and eight miles long in order to prevent grazing in this region.

The cause of milksickness has been attributed to a great variety of intoxicating principles at various times. The mystic miasma from swamps, the web of an insect, the dew on the grass, impure air, impure or stagnant water, a yeast, a mineral rising from the soil and collecting on the leaves of plants, various metallic minerals such as arsenic, copper, mercury, cobalt, barium and aluminum, have all been exploited at one time or another by their adherents.

Poisonous mushrooms were suggested by Winans (13) as the cause of milksickness while Slack (14) held that trembles was due to a parasitic fungus, similar to ergot, that grew on swamp grasses and he suggested the name "Ergdeleteria" for the poisonous principle. Nagle (15) was also of this opinion.

As early as 1856 the microbic theory of causation was promulgated and at different times various organisms have been associated with the disease. In recent years most exhaustive studies tending to support this view have been made by Jordan and Harris (3). In their investigation a new organism was isolated to which they gave the name *Bacillus lactimorbi*.

When cultures of this organism were fed to dogs and rabbits symptoms resembling milksickness were induced.

These observations were not confirmed by Luckhardt (16). In commenting on their results Jordan and Harris say: "taken as a whole, the facts do not surely indicate that a specific microorganism is the cause of the milksickness or trembles."

Of recent years the cause of the disease has been ascribed, on seemingly good grounds, to a toxic agent derived from poisonous plants, particularly from white snakeroot (*Eupatorium urticaefolium*) and the rayless golden-rod (*Aplopappus heterophyllus*). Animals are known to be affected by these plants and the malady is transmissible to man and other animals by feeding on the flesh or milk of diseased cattle. For this reason the theory of a transmissible virus was proposed, although the production of the disease through the inoculation of blood, flesh, milk or other secretions has never been accomplished. Nor is the theory of infection any longer needed to explain the occurrence of the disease, as it has been shown that the *materies morbi* can pass through the milk and thus poison man through the use of dairy products made from the milk of animals that have grazed on the dangerous plants.

Among the earliest feeding experiments in which the poisonous nature of *Eupatorium urticaefolium* was demonstrated were those of Rowe in 1839, who fed the plant to animals with fatal results. Subsequently Barbee confirmed this observation and in 1855 Vermulya (17) produced trembles in sheep and horses by feeding white snake-root. In the report of this work he also pointed out that people were only affected when they used milk from cattle afflicted with the disease.

More recently, investigation of the poisonous nature of white snake-root has been carried out along modern scientific lines, and numerous workers have established the close relationship between consumption of the plant, the appearance of trembles in cattle, and milksickness in man.

Moseley (18) was perhaps the first to make a systematic

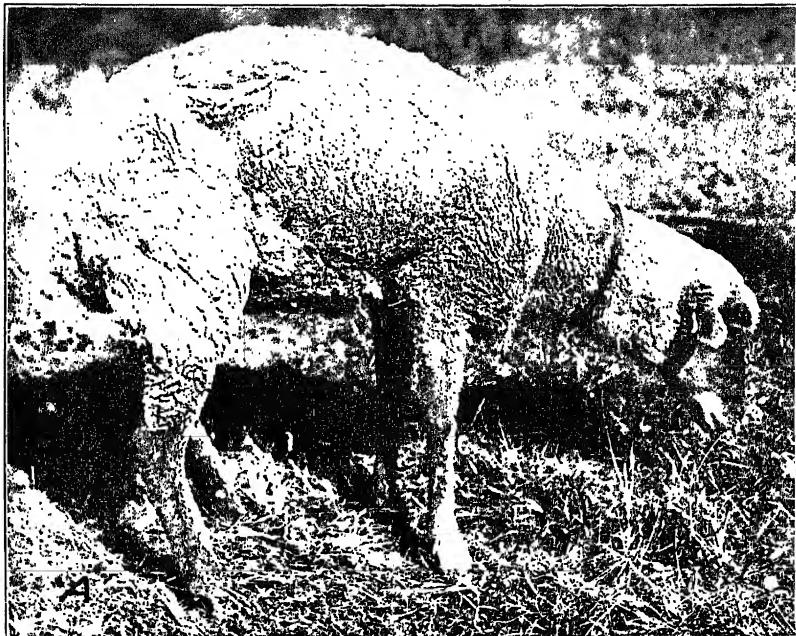


FIG. 14. EWE IN A CHARACTERISTIC STANDING POSTURE ASSUMED WHEN THE ANIMAL IS SEIZED WITH A PAROXYSM OF TREMBLING. AFTER CURTIS

study of the etiology of trembles, and he showed that rabbits, cats and dogs were all susceptible to the poisonous principle present in watery extracts of white snake-root. Sheep fed on fresh leaves of the plants also developed the disease and rabbits injected subcutaneously with an extract of the leaves, exhibited typical symptoms. Subsequently Moseley (19) got the same results in rabbits by feeding aluminum phosphate and upon analysis he found considerable quantities of this salt in both the rayless golden-rod and white snake-root. Aluminum was also found in the milk of a cow fed white snake-root as well as in the urine, liver, kidneys and muscle of rabbits fed this plant. Incidentally, the milk from the cow and the flesh from the rabbits—both raw and cooked—produced trembles when fed to cats. From these observations Moseley concluded that trembles are due to aluminum phosphate and that animals were poisoned by the salt present in the leaves of white snake-root and rayless golden-rod.

Curtis and Wolf (20), in an attempt to confirm the observation made by Moseley, carried out feeding experiments using white snake-root and aluminum phosphate. With the plant they produced typical symptoms in 15 sheep, of whom 14 died, but in those tests in which the salt was fed, no harmful effects were observed.

Marsh and Clawson (21), Sackett (12), and Graham and Boughton (8), have added further to our knowledge of the poisonous nature of *Eupatorium urticaefolium* and at the present time there seems little reason to doubt that this or similar toxic plants is the cause of trembles in cattle and milksickness in man. As further evidence of the implicity of these plants we have the common observation that trembles is most frequently seen during the months of August to October, when these plants flourish, that the herbivorous animals are always affected first, and that the clearing of land or isolation of areas where the plants are common leads to the disappearance of the disease.

SYMPTOMATOLOGY

Onset of the disease in animals is preceded by a prodromal period of intoxication of two to five days, during which the movements of the animal become markedly slower, a faltering gait develops and there is extreme constipation. Following this the muscles become hard and stiff, the extensors being partially paralyzed, and frequently the neck becomes twisted to one side. Very soon muscular weakness sets in and on exertion the characteristic trembling becomes evident. The eyes are at first protruding and glaring, but later become red and covered with a yellowish discharge, while the breath has the odor of acetone. In some instances there may be a discharge of bloody mucus from the rectum. Weakness is very pronounced, the joints become stiff, and often the animal sinks to the ground where it remains for hours at a time, apparently unable to rise. The abdomen is distended and usually there is a fetid odor about the body. The temperature remains normal or slightly subnormal, the pulse is irregular, and respiration is of the Cheyne-Stokes type.

In man some clinicians have professed to distinguish an acute and subacute form of the disease. In either type of the disease there is considerable variation in the length of time necessary for the development of symptoms. Some observers have reported the occurrence of symptoms within a few hours after the ingestion of milk from affected cattle, while in other instances no untoward effects became manifest for a day or two.

In the acute form of the disease there is pallor with flushed cheeks and very red lips. The temperature is not elevated, the pulse but slightly accelerated, and respiration is about 18 per minute. As the intoxication progresses the pulse quickens and the blood pressure drops, respiration continues at about the same rate, takes the form of air hunger and is gasping. The breath carries the odor of acetone. The pupils of the eyes are dilated but respond to light and accommodation. The tongue is scarlet and slightly tremulous, the lungs are not affected, while the heart sounds, which are pounding early in the disease, become

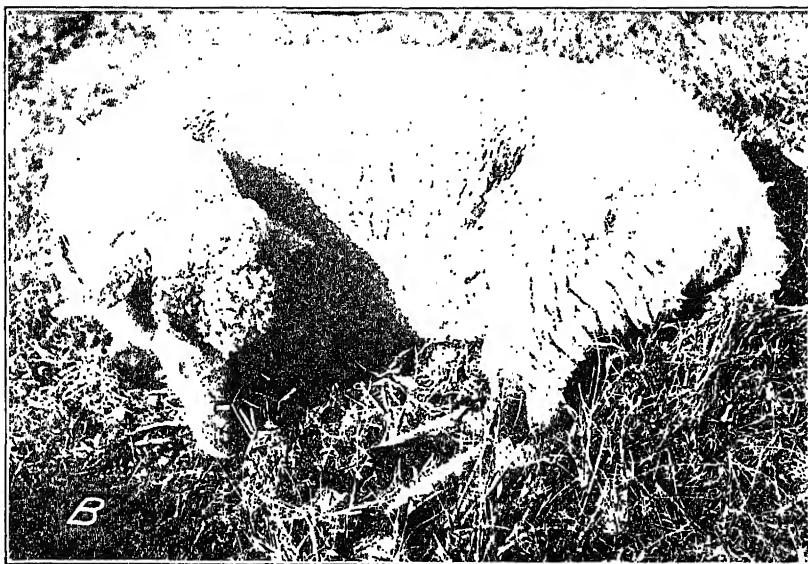


FIG. 15. EWE IN A CHARACTERISTIC RESTING POSTURE AFTER A SPASM OF TREMBLING

Note that the eyes are closed, the ears droop, and the chin is resting on the ground. After Curtis.

faint as the poisoning progresses. The abdomen is soft and not tender on palpation and peristalsis is neither seen nor felt. The deep reflexes are weakened symmetrically, there is no ataxia, muscular weakness is profound, and the muscle tone poor. The appetite is quickly lost, there is nausea, vomiting is persistent, there is marked constipation and the patient becomes increasingly irritable. In two or three days the patient becomes dull and apathetic, the urine is scant and highly colored, has a high specific gravity and usually reeks of acetone. Hiccough frequently follows the vomiting spells and in fatal cases coma precedes death. In the less acute cases convalescence is established when fluids given by mouth are retained. The intoxication is known to recur and when such is the case the attacks may last for weeks at a time.

The following case report by Wilkinson (9) is of interest as an example of this type of intoxication:

"M. X., a white school girl of 17 years, became ill while on her way to school, with nausea and vomiting. She was scarcely able to make the trip back to her home on account of the weakness in her extremities. Going directly to bed, she continued to vomit all that day and night. The bowels did not move, the urine was scant, she experienced no pain except in the epigastrium, which was not severe, but complained as she tossed about in bed that she could not find a comfortable position. The second day she could retain no fluids, though her thirst was great. She continued vomiting and the bowels did not move. The patient was seen by the writer on the third day of her illness. She was lying in the dorsal position, apathetic and could be aroused with difficulty. The cheeks were flushed, lips parched and cracked, the tongue red and coated. The breath was heavily scented with an odor like acetone. The temperature by mouth was 97.6, the pulse 120, systolic pressure 90, diastolic 68, respiration deep and gasping like 'air-hunger.' The lungs were clear. A short systolic blow replaced the first heart sound. The abdomen was soft but tender along the costal margins. The deep reflexes remained unaffected. The laboratory findings showed no conspicuous deviation from the normal except in the urine where acetone and diacetic acid were found in abundance together with a trace of albumin.

"A pint of thick home-made molasses was given by rectum every four hours for one day. The following day great improvement was manifest. The breath was no longer scented and the patient was able to retain fluids. The urine showed a trace of diacetic acid. Convalescence was rapid, the patient being able to be up and about on the eighth day of her illness. The weakness in the extremities persisted for several months."

DIAGNOSIS

The continuous vomiting, extreme weakness, subnormal temperature, and marked constipation are the outstanding features of this disease. The peculiar odor about the body, the presence of abundant acetone in the urine, the high specific gravity, the presence of diacetic acid and beta-oxybutyric acid, but *no* reducing substance, also aid in establishing the diagnosis. Finally, the presence of trembles among cattle from which the milk supply or dairy products have been derived may be regarded as an additional help in determining the nature of the affection.

THE POISONOUS PRINCIPLE

The nature of the poisonous principle in the leaves of white snake-root and rayless golden-rod, that gives rise to the toxic syndrome of trembles in cattle and milksickness in man, is unknown. Moseley (18), was able to extract it with water and Graham and Boughton (8) were equally successful in extracting it with this solvent, although Sackett (12) was unable to extract it with physiological salt solution. Sackett did succeed in obtaining it when he used 95 per cent alcohol or a mixture of ether-chloroform and ammonia. Graham and Boughton also showed it in the residue of the alcoholic extraction of leaves of white snake-root. Wolf, Curtis and Kaupp (22) believe the active principle is a glucoside, while Couch (23) considers that the affected individuals suffer from an acidosis, although the appearance of acetone in the expired air, blood, and urine only *after* the onset of trembling, led him to believe that ketogenesis may be a secondary effect of the intoxication.

PATHOLOGY

In the literature few post-mortems studies are recorded. There are no characteristic lesions and the principal changes are seen in the kidneys, liver and heart, where fatty degeneration and hyperemia are marked.

In the kidneys much blood is usually seen. An inflammatory reaction, accompanied by some edema and occasional punctate hemorrhages, appears in the mucosa of the upper small intestine, especially in the region of the duodenum. In animals—cattle and horses—the edema is more pronounced and is accompanied by the secretion of a quantity of thick bile-stained mucus. Some inflammatory nodules have been observed in the sub-mucosa of the horse and sheep and in some instances they have been seen to ulcerate. The brain in cattle, is congested and there are petechial hemorrhages in the meninges; similar hemorrhages may be observed below the serous membranes all over the body.

Microscopic examination of tissue indicates that the greatest changes take place in the liver and kidneys, where a marked cloudy swelling of parenchymatous cells is seen, generally accompanied by fatty changes which are especially notable in the liver. At times these changes may be so extreme as to make recognition of the tissue difficult. The kidneys show frequently a combined glomerular and parenchymatous nephritis with or without fatty degeneration. Some fatty changes may also be found in the heart muscle. In the intestine much round-cell infiltration may be observed in the areas which are hyperemic and edematous. No changes are noted in the central nervous system.

TREATMENT

There is no specific treatment for milksickness but alcohol is a favorite remedy. In those areas where the disease has been common one of the most frequently employed home remedies is a mixture of whiskey and honey. While based on the grounds of experience alone, such therapy may be well founded as Clay maintains that the poison has an affinity for alcohol. The use of sodium bicarbonate has also been advocated to counteract the acidosis. At the same time a high enema should be administered in order to rid the intestine of any ir-

ritating material that may be present and efforts should be made to maintain the body temperature.

In the cases treated by Wilkinson prompt relief from the acute intoxication was obtained by rectal administration of a pint of thick molasses (glucose) every four hours until the symptoms abated. In these cases marked improvement was observed the day after this treatment was begun and by the third day fluids were retained and convalescence was rapid.

It is to be remembered that such gastro-intestinal symptoms may be only the first manifestation of a true infection with organisms of the typhoid, para-typhoid, or Gaertner group. Consequently the stools should be subjected to a searching examination for these bacilli. Coincidently a sample of the patient's blood may be examined for agglutinins for these organisms.

POISONING FROM DECOMPOSED MILK

Poisoning from decomposed milk, which was formerly much more commonly reported than at the present time, has been called *galactotoxismus* by Vaughan and Novy (24) and has been attributed to the consumption of milk which has undergone putrefactive decomposition. In the cases reported by Vaughan and Novy the symptoms were those of gastro-intestinal disturbance, vomiting, diarrhea, severe abdominal pain, stupor, rapid but weak pulse, more or less dilatation of the pupils of the eyes, rapid though labored respiration, difficulty in swallowing, and great prostration. Similar observations are reported by them to have been noted by Newton and Wallace, at Long Branch, in 1886, by Firth, an English Army surgeon in India, in 1887, and by Schearer in Corning, Iowa.

In such cases of poisoning it has been customary to attribute the illness to a poisonous ptomaine called by Vaughan *tyrotoxicon*, and detected by him in cheese. This ptomaine was produced in the milk as the result of excessive bacterial contamination. All sorts of milk products have been implicated in similar outbreaks and *tyrotoxicon* was detected by Wallace and

Doolittle in cheese, and by Vaughan and Novy, and by Schearer, in ice cream, while Vaughan and Perkins obtained another toxic substance, as well, from the food examined.

Under certain circumstances it may be that occasionally otherwise perfectly harmless organisms growing in excessive numbers in milk may give rise to poisonous products and thus cause acute gastro-enteritis in man. Instances of this character have been reported by Barber (25) in which a white micrococcus growing in milk and cream was held responsible for the outbreak, and by Linden, Turner and Thom (26) in which a streptococcus in certain cheeses was supposed to be the cause of illness. Flügge (27) was of the opinion that the ingestion of milk heavily contaminated with spore-forming organisms which might vegetate in the intestine and produce putrefactive products, might result in irritation of the intestinal mucosa and thus have a bearing on the production of gastro-intestinal disturbances.

On the other hand, under certain conditions, there may be a heavy growth, in milk, of resistant, sporebearing bacilli, that produce true toxins, as shown by Ford and Lawrence (28) for *Bacillus welchii* and such substances may well play a rôle in poisoning of this character.

At the present time the view that poisoning from milk or milk products is due to ptomaines in the milk is generally discarded. More and more evidence is accumulating tending to show that persons who become ill after consuming various milk products are suffering from an infection with typhoid, para-typhoid, or Gaertner bacilli.

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CHAPTER XI

POTATO POISONING

General considerations. Symptomatology. Etiology. Extraction and Identification of Solanin.

GENERAL CONSIDERATIONS

A number of plants belonging to the *Solanaceae* contain under various circumstances, a glucosidal alkaloid—*solanin*. In the potato—*Solanum tuberosum*—the shoots, haulms and leaves contain varying amounts of this alkaloid and there may be sufficient accumulation, at times, to produce poisoning. A considerable number of epidemics of food poisoning have been attributed to the consumption of potatoes that contained much more than the normal amount of solanin.

The majority of cases of potato poisoning have been reported from the European Continent, although Great Britain and Ireland have not been without their epidemics and recently a case was observed by Roberts (1) in Missouri, in the United States.

One of the very earliest outbreaks of potato poisoning in England was reported by Banks (2) and in this instance four members of a family of seven were attacked. Other more or less extensive outbreaks of poisoning attributed to potatoes have been reported by Cortail, Schmiedeberg, Pfuhl, Dieudonné, and Harris and Cockburn. A feature of these epidemics is the fact that by far the largest number of cases have occurred among troops, and that really the only important epidemic among the civilian population is that observed in 1917 by Cockburn and Harris.

In the outbreak reported by Cortail (3) in 1889, the victims were soldiers in garrison, among whom 101 men were affected, while in the epidemics described by Schmiedeberg (4) 716 individuals, distributed among four garrisons, were poisoned.

In these four outbreaks 90 men were poisoned in one instance, in another 125, and in a third 43, while in the fourth epidemic there were 357 cases. None of these cases resulted fatally. A few years later Pfuhl (5) described an outbreak among the soldiers of the Berlin Garrison involving 56 men, while more recently Dieudonné (6) has described a somewhat similar epidemic among the soldiers at Himmelburg in which 150 to 180 cases developed. In 1917 Harris and Cockburn (7) observed 61 cases in the Eastern District of Glasgow, of which one resulted fatally. On postmortem examination it was shown that death in this case was probably due to strangulation of the bowel resulting from violent retching and vomiting.

SYMPTOMATOLOGY

In general, the symptoms observed are those of gastro-enteritis—vomiting, diarrhea, colicky pains, headache, depression, tenderness and pain in the anus and rectum, suppression of the urine, and collapse, and are accompanied in some cases by coldness of the surface of the skin, hallucinations, and coma. The epidemic described by Pfuhl exhibited the above symptoms together with jaundice, a feeling of irritation in the throat, and partial paralysis in a few cases. The symptoms usually appeared within a few hours after the meal of suspected potatoes and the attacks lasted for two or three days.

ETIOLOGY OF POTATO POISONING

In the absence of any definite information as to the active principle causing potato poisoning, it has been usual to consider these cases as due to the greater or smaller amount of solanin known to be present in the tubers. That there is some justification for this conclusion seems to be indicated by the fact that solanin is the active principle of other poisonous species of the *Solanaceae*, as for example, *Solanum nigrum* or the "deadly nightshade," and *Solanum dulcamara*, otherwise known as "bittersweet."

In some epidemics, at least, it has been shown that the con-

tent of solanin in the potatoes was considerably above normal. Such outbreaks are those reported by Pfuhl, in the Berlin Garrison, by Rothe in Leipzig, and by Harris and Cockburn in Glasgow. In these cases the solanin content of potatoes from the same lot as those that caused poisoning was found to be from 4 to 6 times the usual amount detectable in normal tubers.

According to Meyer (8) the solanin content of potatoes varies with the season, from about 0.04 gram per kilogram in winter, to approximately 0.116 gram per kilogram in summer. In diseased or sprouted tubers the content may be considerably increased, as was found by Meyer, Pfuhl, and Harris and Cockburn. As Rothe (9) has shown that it takes 0.2 to 0.4 of a gram of the isolated alkaloid to cause poisoning, it would seem difficult to attribute the illness in all cases to solanin in the potatoes, but where the content has been shown to be several times the normal amount the evidence is more convincing. A case in point is the Glasgow epidemic, observed by Harris and Cockburn, in which the solanin content was determined as 0.41 gram per kilogram of tubers.

Of recent years some doubt as to the production of potato poisoning by an alkaloid has been expressed by various writers, notably Savage (10). These authors are more inclined to believe that the potatoes causing illness are highly decomposed, and therefore heavily infected with microorganisms, and that toxic products of bacterial growth or actual bacterial infection may be the cause of the sickness. That there may be some grounds for taking this position is indicated by the bacteriological investigation of the epidemic described by Dieudonné (6) in the Himmelburg garrison. In this case, the outbreak was attributed to potato salad, and from this Dieudonné isolated a strain of *Bacillus proteus* which killed mice fed on potato inoculated with the organism twenty-four hours previously. Other mice fed on the salad also died with severe gastro-intestinal symptoms. Savage also points out two things that further indicate the possibility of bacterial infection, first, the

symptoms are those of ordinary food poisoning from infected milk, meat, etc., second, the frequency with which peeled cooked potatoes are kept for twenty-four hours or longer before being eaten. During this time the potatoes offer an excellent culture medium for bacteria and it may be that a heavy bacterial infection results.

EXTRACTION AND IDENTIFICATION OF SOLANIN

The method of Meyer is commonly followed: 500 grams of peeled potatoes are put through a grater and pressed in a muslin cloth with frequent washing with distilled water. After settling, decant and render the decanted fluid alkaline with ammonia and evaporate almost to dryness. Add alcohol and boil, then filter and repeat the alcohol treatment twice. Evaporate again to a small bulk, let stand over night, and filter. Evaporate the filtrate to dryness and digest over night with 250 cc. of water containing about 3 cc. of concentrated sulphuric acid. Solanin is readily soluble in this solution. Filter and wash the insoluble portion with water. Unite these washings with the acidulated water and add an excess of ammonia. This will precipitate the solanin. Raise the temperature to 50°C., filter, wash and dissolve the solanin by pouring hot alcohol through the paper. Evaporate the alcoholic solution, treat with a small quantity of ether, dry in a steam oven and proceed with chemical tests for the identification of solanin.

When dissolved in hot amyl alcohol and then cooled solanin gives rise to the formation of a solid jelly (Blyth) (11) or when a minute amount is heated with a solution of telluric acid in moderately strong sulphuric acid—2 parts of water to 1 of acid—an intense red color develops (Bauer) (12).

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CHAPTER XII

FISH AND SHELLFISH POISONING

I. Fish poisoning. General considerations. Poisoning from fish in which certain organs are poisonous. Poisoning from fish infected with pathogenic bacteria. Poisoning from fish in which a poisonous principle has been elaborated by bacteria. *II. Poisoning from shellfish.* Introduction. Shellfish poisoning with gastro-intestinal symptoms. Shellfish poisoning with nervous symptoms. Diagnosis.

I. FISH POISONING

General considerations

Cases of poisoning in man due to the consumption of fish are not uncommon. Some fish are known to be always poisonous; others are poisonous only during the spawning season; still others may be infected with bacteria that are pathogenic for man; and finally, some instances have been reported in which it was claimed that the fish were infected with saprophytic bacteria that gave rise to substances in the flesh that were poisonous for man. As a descriptive term for the condition resulting from eating any of the above types of fish the word *ichthyotoxicosis* has been employed.

Poisoning from fish in which certain organs are poisonous

Such fish as the various species of *Tetradontidae*, *fugu*, or *Puffers*, and the similar species *Cluppea thrissa* and *Cluppea venonosa* are examples of the type of fish in which the poison is located in certain organs and of the type that is poisonous at all times. For the most part, these fish are confined to tropical waters, particularly in the East Indies and about Japan. According to Remy (1) there are, in the waters about Japan, 12 species of the genus *Tetradon* whose reproductive organs contain a substance that causes poisoning when

ingested by man. In feeding experiments in which these tissues were used, Remy succeeded in producing intoxication in dogs with salivation, frequent and severe vomiting, and convulsive contractions of the muscles. Some cases resulted fatally. A more prompt and more frequently fatal result was obtained when the tissues were macerated and injected subcutaneously.

The exact nature of the poisonous principle involved is as yet in doubt. The extract from the poisonous organs has been called *fugin* and according to Takahaschi and Inoko (2) it resists prolonged boiling and acts like a basic substance with alkaloidal properties. In human cases the action of fugin is to produce an acute disturbance of the nervous and digestive systems resulting in headache, restlessness, salivation, vomiting, paralysis, cyanosis, dilatation of the pupils, and death from dyspnoea. Itakura (3) has found that the toxic substance obtained from fugu exerts a paralytic action on the nerve fibers.

In contrast to poisoning of the type of fugu intoxication, where the poisonous principle is localized in certain tissues, there is the type of intoxication due to such species as *Cluppea thrissa* and *Cluppea venonosa* and certain species of *Scarus*. Whenever these fish are eaten poisoning results, and it has been found that all parts of the fish are equally dangerous. To explain such observations various theories—mostly untenable—have been advanced. According to Gunther the poisonous property is due to Medusae, corals, or decomposing substances upon which the fish feed. The symptoms in these cases are of gastro-enteritis and fatalities are common.

Poisoning from fish infected with pathogenic bacteria

Another type of ichthyotoxicosis has been traced to fish infected with bacteria pathogenic for man. Cases of this kind have been reported by Ulrich (4) in which species of sturgeon, carp and barbel were implicated. In one epidemic Ulrich reported the isolation of *Bacillus paratyphosus* Beta from two

patients, while the blood of four others gave positive agglutination tests with this organism. Abraham (5) has also reported 28 cases of poisoning from eating infected pike. Examination for ptomaines and metallic poisons was negative, while the symptoms resembled those seen in typhoid fever, and an organism of the paratyphoid group (Aertrycke type) was isolated. Similar cases of intoxication from infected fish have been reported from Russia by Sieber (6) who isolated a motile anaerobic, spore-forming bacillus, which she called *Bacillus piscicidus agilis*. This organism was pathogenic for fish, mice, rats, frogs, guinea-pigs and dogs, and in its growth in culture media produced methylmercaptan, cadaverin and a heat resistant filterable toxin.

In the literature there are also frequent references to epidemics of typhoid fever due to the consumption of infected fish in those countries where fish are habitually eaten raw—particularly in China and Japan.

Poisoning from fish containing a poisonous principle of bacterial origin

Finally, there are instances recorded in which sterile fish flesh has caused poisoning, presumably due to the formation of some toxic principle in the flesh. Konstanoff (7) reported such an outbreak in which the flesh of a sturgeon was held responsible for the death of two individuals. In this case the flesh was found sterile, as it had a salt content of 15.6 per cent, and as no other poisons were detectable it was concluded that bacterial invasion, prior to salting, had resulted in the formation of some toxic principle that remained in the flesh after the salting process.

II. POISONING FROM SHELLFISH

Symptoms of poisoning after eating various kinds of shellfish such as lobster, crabs, shrimp, mussels, oysters, periwinkles and edible snails are not infrequent. In different cases there

may be great diversity of symptoms, but for the most part they indicate a more or less acute gastro-intestinal disturbance or an obvious involvement of the nervous system.

Poisoning with gastro-intestinal symptoms

Combe (8) observed several outbreaks of food poisoning attributed to the consumption of shellfish and reported that the symptoms resembled those induced by a gastro-intestinal irritant. Nausea, vomiting, pain in the epigastric region, tenesmus and rapid pulse were the outstanding features. In these instances the shellfish were apparently in good condition when eaten. There are in the literature, however, reports of food poisoning in which decomposed shellfish have been inculpated. In these cases the first symptoms became manifest within a few hours after the shellfish were eaten and in many instances were acute. Such cases are said to resemble acute alcoholism to a certain extent. In one outbreak thirty persons were thus poisoned, two fatally, with symptoms of nausea, vomiting, a prickly feeling in the hands and feet, constriction of the mouth and throat, difficulty in speaking or swallowing freely, numbness about the mouth which spread to include the arms, slight pain in the abdomen on palpation and great weakness in the limbs. The secretion of urine was suppressed in some and not in other cases, the heart action was feeble, breathing was normal, the expression was anxious, the surface of the body was rather cold, and the mind clear. Post-mortem examination in the two fatal cases showed no abnormalities.

A somewhat similar outbreak of mussel-poisoning occurred at Wilhelmshaven and was reported by Schmidtmann (9) who observed that the symptoms appeared soon or late according to the amount of shellfish eaten. The outstanding features of these cases were constriction in the lips, mouth and throat, difficulty of speech, dilatation of the pupils, lack of headache or fever and a rapid and hard pulse. In addition there was nausea, vomiting, great weakness in the limbs, a feeling

of suffocation, a sensation of coldness in the extremities, which gradually spread over the whole body, and an absence of abdominal pain or diarrhea. Postmortem examinations made by Virchow, disclosed distention in the vessels of all the organs, the absence of blood in the heart, marked hyperemia and swelling of the mucous membranes of the stomach and intestine. The spleen was enormously enlarged, and the liver showed many haemorrhagic infarctions. From these mussels Brieger extracted a ptomaine which he called *mytilotoxin*. Whether this substance should be regarded as responsible for the poisoning seems very doubtful because of the findings of Lindner (10) who showed that the bay water, from which the shellfish were taken, was very highly infected with protozoa and bacteria not ordinarily found in sea water. Furthermore he was able to show that non-toxic mussels placed in this water became toxic and that mussels from this area when removed to clean water lost their toxicity. It appears then that there was at least a chance that they were infected with bacteria that produced substances which were toxic when ingested.

More recently a somewhat similar instance of poisoning was reported by Rolfe (11) in which mussels were gathered from an area of high pollution. After thorough washing and cooking in several changes of water, they were eaten with vinegar and salt. Four hours later the first symptoms appeared. In these cases there was giddiness, mental excitement resembling acute alcoholism, dilatation of the pupils, dryness and constriction in the throat, numbness of the extremities, distention of the abdomen and slight tenderness in the epigastric region. The pulse was full but not increased, the heart sounds were clear and loud, the temperature was normal, and the elbow and knee reflexes were unimpaired. One patient died in syncope with paralysis of the respiration.

Many other instances of poisoning by shellfish from oysters, crabs and lobsters have been reported, but in no case have we any accurate knowledge as to their etiology.

Shellfish poisoning with nervous symptoms

Another type of case is that in which the symptoms are purely nervous. Whether this reaction is a true poisoning or is due to protein sensitivity is open to question. The patient complains of a sensation of heat and itching, especially in the eyelids, and there are a nettle rash, a diffuse edema, asthmatic breathing, dyspnea, lividity, and convulsive movements of the extremities. It may be that the lymphagogue found by Heidenhain (12) in crabs, is responsible for this reaction but this is not settled. This substance cannot be regarded as a decomposition product as it has been repeatedly obtained from fresh tissue, but it is conceivable that under certain conditions it is increased in amount to the point where it acts as a poison.

Diagnosis

As the symptoms are generally referable to the nervous system or to gastro-intestinal irritation the clinical condition is usually well defined. In those cases where the nervous symptoms are especially prominent, there are a sensation of heat and itching, a diffuse edema, a nettle rash, asthmatic breathing, dyspnea, lividity, and convulsive movements of the extremities. On the other hand, in those cases characterized by gastro-intestinal disturbance, there are nausea, vomiting, pain in the gastric region, tenesmus and rapid pulse. Frequently there are constriction of the mouth and throat, difficulty in articulation and deglutition, weakness in the limbs, feeble heart action, suppression of the urine and cyanosis. In some cases dilatation of the pupils has been observed.

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PART III
ZOO-PARASITIC INFECTIONS ACQUIRED
THROUGH FOOD

CHAPTER XIII¹

HUMAN INFECTION WITH ANIMAL PARASITES

General consideration of human infection with animal parasites. Special importance of the worms in the zoo-parasitism of man by way of food. Reasons for the large parasitic fauna of man. Life histories of worm parasites. Comparative unimportance of protozoa.

Human infection with animal or zoo-parasites, introduced through the medium of food, is of special interest because of the number of helminths and protozoa which are present all, or part, of their lives in the intestine. Their presence in the alimentary canal may thus be looked upon almost as indirect proof of the mouth as the portal of entry, and such is generally the case. Moreover, in addition to the large number of intestinal forms, there are many tissue infections by zoo-parasites, outside the intestine, in which the parasites gain entrance to the host through the agency of food. Indeed, except for the skin-penetrating worms—*infection with which may conceivably occur via the mouth*, although under natural conditions this seldom takes place—the parasites which enter the skin through the aid of an insect intermediate host, and the malarial and other blood-inhibiting protozoa, human helminthology and protozoology may be thought of as concerned primarily with organisms that gain entrance to the host through the mouth. This mode of entry may be either necessarily or incidentally accomplished through the agency of food or water, as well as by the direct transfer of the infective agents to the lips by soiled fingers.

For the most part the life histories of animal parasites in their relation to man are of two types. Many of them re-

¹ It is a pleasure to acknowledge the valuable aid offered by Dr. Norman R. Stoll in the preparation of Chapter XIII.

semble in a way some bacterial infections. For example, in certain instances the parasites, already resident in the intestinal tract of one person, are by fecal contamination of food or the fingers transferred either to a new host, resulting in a newly infected individual or to the same host, causing an increase of infection of the original kind in the original host. In such cases the parasite has a life history in which no second type of host is required for the completion of the life cycle and secondary infection is only necessary for the perpetuation of the species. This is the case with *Enterobius (Oxyuris) vermicularis*, the common pin or seat worm of man. Contrasted with this simple process of direct transfer of infective material from person to person is that process in which the contaminative material of the worm parasite—usually an egg—requires a certain amount of development in the environment before becoming infective, as with *Ascaris lumbricoides*, the large round worm of man. Here again, however, the life cycle of the parasite requires no intermediate host for its completion.

Another, and even more interesting group of worm parasites has a somewhat more complex life history. That is, in their life cycle it is essential that they undergo development through a certain stage in one host, and then in order to complete the life cycle they must develop a new stage in a second or even a third host, often these successive hosts being of very different types, as fish, snails, or men. In a few species man may function as the intermediate as well as the final or definitive host. Such infection of man with the intermediate stage of the parasite, however, is usually in the nature of a "blind alley" infection, as no further continuation of the species is possible in the absence of the consumption of human flesh by a susceptible animal. A case in point is the infection of man with the larval stage of the armed or pork tapeworm, *Taenia solium*.

Moreover, for those parasites of man in which he acts as final host infection is necessarily acquired by means of certain substances which enter the mouth primarily as foods, and which may differ with the various parasites.

SPECIAL IMPORTANCE OF WORMS IN THE ZOO-PARASITISM OF
MAN BY WAY OF FOOD

The parasitic worms are of special importance in the study of human zoo-parasitism. This is true, not only because of the number of valid species that have been described from man, but particularly because of the abundance of illustration which they furnish by which zoo-parasitism *per os* may be and is accomplished. By comparison, the protozoa as a group, and the arthropods of incidental importance, merely serve as additional examples of types of infection common among certain of the helminths.

In the discussion of the subject that is to follow, attention will, therefore, be particularly directed toward the helminthic parasites, not only because they are more numerous, but because they illustrate the essential factors involved in a consideration of other forms. However, mindful of the method of approach to the discussion of the other subjects considered in this book, interest here will be particularly directed toward a general survey of the problem of human zoo-parasitism, chiefly from the standpoint of the geographical distribution, methods of infection, prevention of infection, and diagnosis of the various parasites.

REASONS FOR THE LARGE PARASITIC FAUNA OF MAN

Before taking up the bearing of the general types of helminth life histories on the problem of human zoo-parasitism, some consideration may well be given to certain facts which aid in making clear the reasons why such a large parasitic fauna has been described from man. One such fact is encountered in the overlapping food habits of man and animals with the consequence that the same potential sources of infection are open to both. As a case in point the potential danger to men and animals, such as cats and dogs, of eating fish infested with the larvae of the broad tapeworm *Diphyllobothrium latum* may be cited. This is one of many instances of overlapping food

habits that might be given. It is not surprising, therefore, to learn that many of the parasites which have been described from man are common in or at least known as typical of other animal species. Conversely, some of the forms that are ordinarily found in other animals have been reported so often from man that they may be considered primarily parasites of human beings. The fact is, however, that man merely shares with other hosts the distinction of commonly harboring the parasites, thereby assisting to keep up their life cycle more easily. Man is thus to be thought of as well adapted to maintain some of the more truly animal parasites. But such is not always the case; in some instances infection of man appears to lead the parasite into a "blind alley" from the standpoint of maintenance of the species. Human infection with the larval stage of the pork worm *Trichinella spiralis* illustrates this point.

Another fact which has helped to swell the total of known species of helminths described from man is their relative size. Even the typically smallest stage in the life cycle of a parasitic worm—the egg—is many times larger than the bacteria, for example, and in the microscopic examination of fecal material would therefore attract attention. From this it follows that recognition of zoo-parasitic infection has been more easily accomplished, and has therefore attracted the attention of clinicians and investigators. A corollary to the above consideration is the fact, that due to their gross size, infestation by a single or at most, a few worms is occasionally all that is necessary to produce more or less serious injury to the host. Consequently, many species of helminths are known from man which have been reported only a few times in medical history.

LIFE HISTORIES OF WORM PARASITES

Before considering the several species of parasites to be discussed, it will be well to review briefly certain generalities in the life history stages of the parasitic worms. Helminths fall into three great classes, namely, the *Trematoda*, or "flukes," the *Cestoda*, or "tapeworms" and the *Nematoda* or "roundworms."

A fourth class, the *Acanthocephala* or spiny-headed worms, do not indubitably occur as human parasites and may be omitted from consideration.

So far as is known, all human infestations with trematodes are with man as the final host. The trematodes thus furnish some of the best examples in which man becomes parasitized, in obligate fashion, through food.

Trematode life history. The life histories of flukes typically involve a molluse, usually a snail, as the first intermediate host. From the snails, larvae, or cercariae, emerge, which may directly penetrate a final host, as in the case of the schistosomes or blood flukes. In such a case human infection by way of food or the mouth is not a problem.

On the other hand, in other species, the cercariae may encyst on water plants, as with *Fasciolopsis*, or in the tissues of a second intermediate host, usually fish or aquatic arthropods, as is the case with *Clonorchis* and *Paragonimus*. The infection of the final or definitive host, in which the worm again reaches its adult stage, then becomes a matter of ingestion of infected food stuffs, or more rarely of water into which the intermediate hosts have released the still infective encysted cercariae. For all practical purposes the latter method of entrance may be neglected in a consideration of the usual mode of human infection.

Cestode life history. The life histories of the tapeworms are somewhat less involved than those of the flukes, although here again they include, with few exceptions, an intermediate host stage.

In the case of these worms, the "eggs" which escape in feces are immediately infective—with the exceptions of the group to which the broad tapeworm, *Diphyllobothrium latum*, belongs—inasmuch as they inclose an embryo which when released in the digestive tract of another animal, pierces the intestinal wall and migrates to the tissues. The intermediate hosts of the cestodes include arthropods and vertebrates, usually mammals. In the case of an arthropod intermediate host,

the young tapeworm embryos usually develop in the body cavity, as is the case with *Dipylidium caninum*, the dog tapeworm, which occasionally infests man. In contrast, when the vertebrate acts as the intermediate host the larval stage exists as a tissue parasite, as for example in infestations with *Taenia saginata*, the beef tapeworm. Occasionally both arthropod and vertebrate hosts are included in the same life cycle. Such is the case with *Diphyllobothrium latum*, the broad or fish tapeworm of man, but this is unusual.

The fact that mammals may act as intermediate hosts makes the danger from cestode infestation in man a double one, in that he may function in their life histories as either an intermediate or definitive host. In fact the gravity attending cestode infestation of man is more with the intermediate, than the final stage, for with the latter, the intestinal tract alone is parasitized as a rule, whereas the intermediate stage may involve tissue parasitism in practically all parts of the body. An exception must be made here of parasitism with *Hymenolepis nana*, the dwarf tapeworm of man, however, as the intermediate stage is passed only in the villus of the intestine.

Under ordinary circumstances a given cestode species infests man either in the intermediate or adult form exclusively. Thus hydatid disease represents the larval infestation of man with the dog tapeworm, *Echinococcus granulosus*, the adult not occurring as a human parasite, while *Hymenolepis diminuta*, one of the rat tapeworms, is an adult tapeworm, the larval stage of which is never found in man.

At least one of the cestode species may use man as a host for either the larval or adult stage. In this case, as before stated, infestation with the larval stage is the more dangerous. In such instances in which man may act as host for either the larval or adult stage it seems quite certain that autoinfection with the larval stage may occur, once man harbors the adult parasite. This is held to be true with *Taenia solium* the so-called armed or pork tapeworm of man. Due perhaps to vomiting, eggs from the adult *Taenia solium* in the intestine,

are carried up the intestinal tract, by reverse peristalsis, to a point where the young embryo is assisted by the digestive juices to escape from the "egg-shell." It then promptly penetrates the intestinal wall and getting into the circulatory system is carried by the blood stream to remote parts of the body, and infections are known from the brain, pancreas, liver, eyes, lungs, heart, etc. Such infestation can also be brought about by directly swallowing the "eggs" of the parasite in contaminated food.

A few of the cestode parasites of man are known only as larval forms, the adult stage and host being as yet not recognized. Among these are the *Sparganum* species, tissue parasites, which are probably analogous to the plerocercoid larvae of *Diphyllobothrium latum*, the fish tapeworm of man, which possibly gain entrance to their human host, either through the ingestion of a first intermediate host such as Cyclops, or through fish, frogs, or mammals which contain the second stage larvae.

From these considerations it is obvious that cestode life histories thus furnish a greater variety of methods of infection than is the case in the trematodes, and their prevention, as a group, is theoretically less simple.

Nematode life history. It is among the nematodes or roundworms that the greatest diversity in the life history occurs. In these species there may or may not be an intermediate host stage.

Among those species of roundworms in which there is no intermediate host stage, the adults in the human intestine give off eggs which are immediately infective. These eggs, swallowed by the same or another person are thus capable of transmitting the infection at once and such is actually the case with *Enterobius (Oxyuris) vermicularis*, the pin or seat worm of man.

In contrast to the above, the eggs from an adult worm, already established in the intestine of a human host, may require a period of external development of even several weeks, before becoming reinfective after mouth passage. Infections with

Ascaris lumbricoides, the large round worm, and *Trichuris trichiura* (*Trichocephalus dispar*), the whip worm of man, illustrate this point. On the other hand, an intermediate host may be required, which in some cases is an arthropod, as with *Dracunculus medinensis*, the guinea worm of man, which has a required larval stage in the Cyclops, a fresh-water crustacean. In other instances the required intermediate host stage occurs in mammalian tissue as in *Trichinella spiralis*, the pork worm. The situation with *Trichinella spiralis*, however, is rather a special one, inasmuch as a parasitized individual really acts as both intermediate and final host, ingested meat containing the larval forms permitting the establishment of an adult stage of the parasite in the intestine, where the worms do no striking harm while raising a brood of young larvae which immediately penetrate the intestinal wall and end up as muscle parasites in the same host. From the standpoint of the organism, then, human infestation with the larvae of *Trichinella spiralis* leads it into a "blind alley," in the absence of human cannibalism to permit the next transfer of the parasites.

With these facts in mind it becomes evident that the danger of infection from nematode parasites, which may be contracted from food, is thus primarily from species which utilize man as a final host with the single important exception of *Trichinella spiralis* noted above.

COMPARATIVE UNIMPORTANCE OF PROTOZOA

The protozoa which infect man via the mouth, perhaps usually by food, have typically cyst or trophozoite stages in the feces, depending on the protozoan species involved, and these are immediately reinfective. These cyst stages also are undoubtedly infective for some time thereafter, but as far as known there are neither obligate nor optional life history stages in other animals, although further investigation may reveal reservoir hosts. Infections with protozoa, from the standpoint of our present interest, therefore, parallel those with nematodes which do not require intermediate hosts.

The importance of human myiasis, that is, infection of the intestinal tract with insects, especially insect larvae, is so inconsiderable as not to merit special discussion here. Such "infections" appear to be primarily from intestinal passage of fly larvae which are in or on partially decayed food. Apparently there are no species which are either obligate or even frequent, human parasites.

The outstanding importance of human infection with certain species of the cestodes or tapeworm, such as *Taenia solium*, *Taenia saginata*, and *Diphyllobothrium latum*, and the nematode worm *Trichinella spiralis*, warrants their consideration separately and in some detail in the chapters to follow.

CHAPTER XIV

TRICHINOSIS

Historical. Occurrence of the infection in lower animals. Life history of the parasite. Symptomatology. Laboratory diagnosis. Differential diagnosis. Pathology. Mortality. Treatment. Prophylaxis.

HISTORICAL

The disease known as "trichinosis," or "trichiniasis," is an acute, specific infection due to the invasion of the muscles by the embryos of the nematode worm *Trichinella spiralis*. The condition is characterized by remittent fever, edema of the face, eosinophilia, emaciation, and local pain and soreness in the muscles involved.

There is considerable evidence indicating that the ancient Jewish edict against eating pork was inspired, at least partially, by the common infection of such meat with the larvae of this worm. However, conclusive evidence of the connection between consumption of trichinous meat and development of the disease in man, the elucidation of the life cycle of the worm, and thorough study of the clinical condition was never recorded until relatively recent times.

The first observations of encysted larvae in the muscle tissue of man seems to have been made by Tiedman in 1821, and Hilton, about ten years later, apparently first suggested that they might be parasites; evidence to support this view was not forthcoming until some thirty years afterward. In 1835, Paget recognized the encapsulated larvae as those of a nematode and submitted some of his material to Owen (1) who described the parasite in detail, and gave it the name *Trichina spiralis*. Subsequently, the name was changed to *Trichinella spiralis*, as it was found that *Trichina* had been previously used for another species.

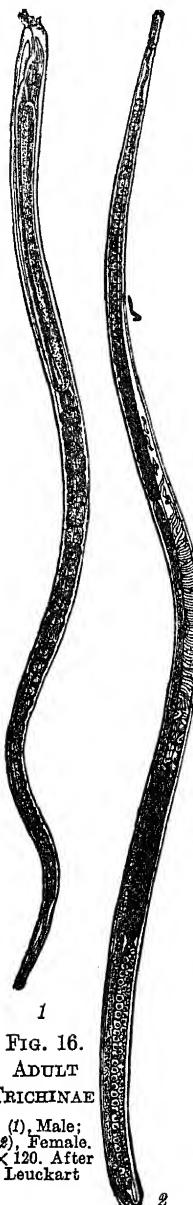
The first published descriptions of the worm, as occurring in the United States, seem to be those of Bowditch (2), who recognized the parasites in man in 1842, and Leidy (3) who found them in the meat of hogs in 1847.

These encysted forms were, for a long time, thought to have no pathological significance, until the experimental work of Herbst (4) demonstrated that by feeding meat containing the worms to a normal animal, an infection could be produced. The first serious consideration of their possible pathological significance in man resulted from the description by Zenker (5) of his classical case in Dresden in 1860. Subsequently, his studies together with those of Leuckart (6), Virchow (7) and Küchenmeister (8), led to the elucidation of the life history of the parasite, and definitely connected the appearance of the disease in man with the consumption of infected meat from the hog.

From the clinical aspect it may be noted that the pronounced eosinophilia, which is observed as one of the characteristics of the disease, was first studied and reported by Brown (9) in 1897.

OCCURRENCE OF INFECTION IN LOWER ANIMALS

The only natural source that is of any real consequence in the infection of man exists in hogs, although under natural and experimental conditions a variety of other animals may be infected. Thus infections have been reported in rats, dogs, cattle, sheep, and horses; in fact, Stiles (10) states that the larvae have been met with in the meat of no less than 25 mammals. Birds, reptiles, fish, and invertebrates, are never subject to spontaneous infection, but may be infected artificially with more or less difficulty. In birds it has been observed that the parasite does not encyst in the muscles, but simply exists in the intestine temporarily and is passed with the feces. In cold blooded animals encystment in the muscles is exceptional, but it has been observed. In general, natural infection is more common among carnivora than in any other species of animals,



while infection among herbivora is more of an accident, due to the consumption of infected material under the stress of unusual circumstances. Such might be the case during periods of famine.

LIFE HISTORY OF THE PARASITE

The organism occurs in three stages, namely, the encysted larva, the adult, and the embryonic form, and the order in which these are discussed may well follow the order of stages in which natural infection takes place.

When trichinous meat is eaten by a suitable host, the larvae in their lemon-shaped cysts are taken into the alimentary canal in the *infective stage*. The action of the digestive juices on the cyst wall, in the stomach, is so rapid that it is entirely dissolved and the larvae set free in the course of a few hours. The young worms then pass to the small intestine, where they grow rapidly and reach maturity in two or three days. Very soon after this, the adult females are impregnated and at once seek to penetrate the intestinal mucosa, lodging between the epithelium and the connective tissue. From this point the embryos escape from the gravid females directly into the mucosa and submucosa of the host. This escape begins about eight days after impregnation and continues for about six weeks, although the female gives birth to the majority of young during the first two weeks of her life. In the meantime the male adults die in the intestine and are eliminated with the feces.

Until very recently two views have been held as to the dispersal of the second or embryo stage of the parasite. By some observers, the dissemination of the embryos has been regarded as an active process in which the parasites bore their way through the connective tissue to their ultimate location. By others, the process has been considered as passive, and the work of Graham (11) seems to indicate that this is the correct explanation. His observations show that the young are carried principally by the lymph stream, that they may also be distributed by the blood and that they may eventually appear in the urine and even in the spinal fluid. In the great majority of cases the final location of the embryos is in the voluntary muscles where conditions are most favorable for their encystment, and it is in these muscles that the most profound changes are brought about. Lodgement of the parasites in other tissues is not uncommon, however, and Van Cott and Lintz (12), Lintz (13), Bloch (14), and Meyer (15), have demonstrated the embryos in the spinal fluid and have observed marked meningeal symptoms. Microscopic examination of striated muscle in which the embryos have encysted shows that it has lost its transverse striation and undergone granular and fatty degeneration.

During the period of migration of the embryos the peculiar symptoms of the disease are most marked, as the embryo encysts, in about 15 days after getting into the muscle, at which time symptoms subside. Here it remains quiescent, although viable, for long periods of time. In fact, such embryos have been found alive even 25 years after the presumed infection. From this point the life cycle of the worm can only be repeated through the consumption of such trichinous meat by man or a susceptible animal.

SYMPTOMATOLOGY

Usually, there is a definite period of incubation which may vary from 5 days to 3 weeks before the first symptoms become manifest. Exceptionally, there may be an acute gastro-intes-

tinal upset almost as soon as meat containing *trichinella* is eaten.

The first symptoms are generally a sensation of heaviness in the epigastric region, nausea, vomiting, mild diarrhea, pain and cramps in the abdomen. The diarrhea may become more severe until the stools are watery and contain bloody mucus; constipation is sometimes observed. The temperature slowly rises for a week to 105°F. or 106°F., and there may be great prostration with stiffness and pain in the muscles. The fever varies greatly in duration and intensity, is usually of the remittent type and nearly always terminates by lysis. In some cases chills or chilly sensations are experienced at the beginning of the disease, and not infrequently there are sweats which persist throughout the illness. The usual accompaniments of a toxic fever, headache, more or less somnolence, anorexia, and loss of weight, are seen in the more severe cases.

The local signs and symptoms associated with the stage of dissemination of the embryos are of considerable importance in the clinical picture. The arms and legs are usually somewhat flexed in order to relieve the strain on the muscles, which are stiff, hard and tender. The muscles of mastication, deglutition, and respiration are especially involved, with disturbance in their function varying from stiffness to pseudo-paralysis. Some cases have been observed in which muscular movement was so painful that no efforts at all were made to change the position and erroneous diagnosis of paralysis was made. In other ambulatory cases, the knees were habitually kept bent and the heels raised.

The movement of the eyes is usually painful, a burning sensation in the eyeball occurs and there may be subconjunctival or subcorneal hemorrhages. In some severe cases marked and persistent dilation of the pupils has been observed. The edema of the eyelids is the most outstanding ocular symptom and is seen in practically all cases.

Frequently, there are cutaneous and subcutaneous lesions that are important, as they resemble those seen in other dis-

eases. In many cases herpes labialis and erythema are seen, occasionally accompanied by general pruritis, and not infrequently skin eruptions on the lower chest or abdomen, papular in type and closely similar to the rose-colored eruption in typhoid fever. There may also be a subcutaneous edema which is most noticeable where cellular tissue is loose, as in the eyelids, but it is not necessarily confined to such areas, as it may be quite widespread over the face and dependent portions of the legs.

The pulmonary symptoms may be so pronounced as to dis-

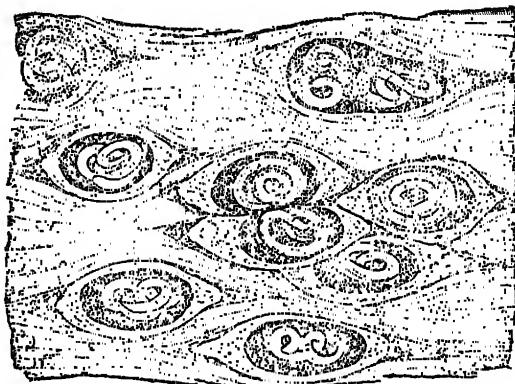


FIG. 17. ENCAPSULATED MUSCLE TRICHINÆ. $\times 60$. AFTER LEUCKART

tract attention from the real cause of the illness. According to some clinicians, the pulmonary symptoms vary from attacks of asthma to definite bronchitis, with or without bronchopneumonia.

There are also cerebral symptoms of greater or less severity, varying from headache and changes in the deep reflexes to delirium.

In severe or protracted cases there is considerable loss of weight, the patient becomes anemic, and cachexia is marked.

As the disease progresses and the embryos encyst, the symptoms begin to abate. The temperature drops and the muscular disturbances subside, but if the case has been severe, the

patient remains anemic and emaciated, while the muscular weakness persists for months after convalescence. In fact, the muscle tenderness may remain for more than a year after recovery. At the same time the ocular symptoms subside and the edema of the eyelids and extremities disappears.

LABORATORY DIAGNOSIS

In addition to the above signs and symptoms, information of the utmost value in diagnosis is obtained by the laboratory examination of blood, spinal fluid, urine and feces. Of these the blood changes are of the greatest significance as Brown (9) observed a leucocytosis which is proportional to the severity of the infection and a differential count shows a marked eosinophilia varying from 10 to 80 per cent. Traces of this eosinophilia may remain for years after recovery.

Occasionally, the embryos may be demonstrated in the circulating blood as shown by Herrick and Janeway (16) by taking 10 cc. of blood with 10 parts of 3 per cent acetic acid, centrifugalizing, and examining the sediment under the low power of the microscope.

The microscopic examination of spinal fluid may also serve to demonstrate the worms, as such examinations have been positive in the hands of Van Cott and Lintz (12), Elliot (17), Salzer (18), and Cummins and Carson (19). At the same time definite changes in the fluid may be observed. Bloch (14), Cummins and Carson (19), and Meyer (15) have observed that it was increased in volume, that the cell count was increased, that the Nonné reaction—indicating an increase in globulin content—was positive, and that Haines solution was reduced, indicating the presence of glucose. This makes it clear that in some cases there are indications of definite trichinous meningitis.

Routine examination of the feces is usually negative, as the female worms penetrate the submucosa of the intestine shortly after impregnation and the males are discharged in an unrecognizable form. Some cases are on record though, in which the

adult worms have been found in the feces, so this method of diagnosis must not be entirely overlooked.

DIFFERENTIAL DIAGNOSIS

In large outbreaks of trichinosis, such as have occurred in Saxony and Prussia, recognition of the disease is not difficult, but in family outbreaks or in sporadic cases, as they come to the attention of the medical practitioner, such is not always the case. Questioning of the patient frequently elicits information of having eaten undercooked pork or pork products, and this, together with the appearance of a febrile disease exhibiting the features of typhoid fever but accompanied by marked edema of the eyelids and soreness and pain in the muscles may be regarded as strong presumptive evidence as to the nature of the disease. Examination of the blood will also demonstrate a leucocytosis accompanied by eosinophilia in nearly all cases. Final evidence, which establishes the diagnosis beyond question, is obtained by demonstrating trichinella in a teased portion of muscle, selected because it was painful, and removed from the region of the tendinous insertion. In such muscle the embryos have been found most plentifully.

There are several diseases in which the clinical picture seen in trichinosis is partially reproduced, but when considered critically there are distinct points of differentiation. The rare disease known as dermatomyositis, which very closely resembles it, has even been called pseudo-trichinosis. In this disease there is a combination of myositis and edema, as in trichinosis, but the absence of eosinophilia, the slight fever, the presence of an erythematous skin eruption on the face in the early stages of the disease, and the absence of edema of the eyelids serve to distinguish the two conditions. In other cases, especially in the early days, trichinosis has been confused with typhoid fever, but the facial edema, muscular soreness, leucocytosis and eosinophilia, the negative Widal reaction, the negative blood and stool cultures, and the non-palpable spleen are points of differentiation.

The marked pulmonary signs have sometimes led to confusion of trichinosis with pneumonia, but the blood picture, together with the edema and muscle tenderness are distinctive.

Of recent years, the observation of marked nervous symptoms has frequently suggested meningitis and it is now recognized that if many embryos reach the spinal fluid and penetrate the spinal and cerebral meninges, there may be a true trichinous meningitis. The obvious edema, the eosinophilia, and the not infrequent demonstration of the embryos in the spinal fluid, render the diagnosis certain.

PATHOLOGY

The macroscopic picture, presented in fatal cases of trichinosis, combines the lesions due to a general toxemia with those attributable to the localized action of the embryos on the muscles of the body. When death occurs quickly after onset, that is, within the month after the appearance of the first symptoms, there is emaciation, edema, especially of the face and extremities, and effusion into the serous cavities.

The lesions in the intestines from the penetration of the parasites into the submucosa are enteritis, congestion of the mucosa, with occasional minute whitish or even ulcerated areas. The intestinal contents consist principally of mucus containing more or less blood, the neighboring mesenteric nodes are swollen, congested, and soft, the liver may be intensely fatty, the spleen little or not at all enlarged, and there may be parenchymatous and fatty changes in the kidneys and heart muscle.

The lungs are frequently congested and edematous, and bronchopneumonia is not uncommon.

The recently encapsulated embryos are not visible until a certain degree of calcification in their capsules has taken place, but when this has occurred, small grayish, more or less translucent areas, representing the encapsulated larvae, are demonstrable.

Ocular changes generally consist of subconjunctival hemorrhages.

Microscopically, the lesions vary with the stage of the dis-

ease. The intestinal mucosa is swollen and the epithelium eroded; later, as the embryos make their way throughout the body there is destruction of tissue in the brain, lungs, diaphragm, heart muscle, pancreas, and in particular, in those muscles that are most active and most open to infection by virtue of their greater blood supply. These lesions take the form of localized hemorrhagic areas, more or less necrotic areas, inflammatory edema, infiltration of the tissues with endothelial cells, lymphocytes, polymorphonuclear and eosinophilic leucocytes.

In those cases recovering from the disease there may be no permanent evidence of the infection. In such cases the embryos lodged in the muscles become surrounded by connective tissue forming the capsule of the worm. Subsequently, calcification results in the formation of a lemon-shaped cyst.

MORTALITY

The mortality rate in trichinosis is usually not high, the average in a large number of epidemics being between five and six per cent. Most of the large epidemics of this disease have been reported from Continental Europe, mainly from the northern part of Germany. Stiles (10) collected data for Germany covering the years 1860 to 1880 and found 8497 cases with 513 deaths, a mortality of about six per cent. From 1881 to 1898 there were 6329 cases with 318 deaths, a fatality incidence of approximately five per cent.

In the United States Ransom (20) reported 1558 cases with 240 deaths during the period 1842 to 1914, thus establishing a death rate of about 13 per cent in this country. However, it is probable that the disease has not been as consistently diagnosed in the United States as in Germany and the death rate may have been even higher than is indicated.

TREATMENT

If the diagnosis is made promptly, during the period of acute gastro-intestinal disturbance or before the impregnated females have penetrated the intestinal mucosa, a thorough purgation

is indicated, as by this means some of the parasites may be eliminated. If the usual period of incubation has elapsed before treatment is begun, purgation may be of little value, as the embryos probably will have penetrated the mucosa and may even be in the general circulation. As the purge can do no harm it should be given, nevertheless, as it is known the parasites may exist for several weeks in the intestine and it may be possible to get rid of a certain number of females that are as yet unimpregnated, or that have not yet penetrated the mucosa.

During the febrile period of the disease the patient should be kept in bed and fed a soft diet of high calorific value, which is easily assimilated. Water may be given freely and if the fever persists, it may be combated by tepid sponge baths or alcohol rubs. The circulatory depression may be relieved by hypodermic injections of caffeine sodium benzoate and the muscular pain relieved by codein or even morphin.

The neutralization of the toxemia by serum therapy has not been altogether satisfactory, although Salzer (18) reported good results in a series of cases. Such a procedure has no effect on the worms themselves, of course, but numerous experiments directed toward their destruction *in situ* have been reported. Tyzzer and Honeij (21) have employed roentgen-rays and radium emanations, and McNerthney (22) used salvarsan and neosalvarsan, but with discouraging results. Such treatment naturally raises the question as to whether the body of the host would be able to resist the wholesale liberation of toxic material resulting from widespread destruction of the parasites by such methods as these. Very recently, Grove (23) has reported success using antimony and potassium tartrate but these results have not been confirmed as yet.

PROPHYLAXIS

Thorough cooking of all pork and pork products so as to ensure the death of encysted larvae, not only in the outer but in the deeper portions of the food as well, is the best way of

preventing trichinosis. In this connection Ransom (20) has shown that exposure to a temperature of 140°F., or holding at 5°F., for 20 days is lethal for the parasites.

From the standpoint of preventing infection in swine, the attention of pork producers must be directed to the danger of feeding pigs offal that may possibly be infected. Sufficient care in this respect will very generally eliminate infection at the source.

Inspection of carcasses in the abattoirs may also help in diverting a certain number of infected animals from the usual channels of commerce, but this procedure cannot be entirely relied upon to detect all dangerous meat and may lead to the development of a false sense of security in the public mind.

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CHAPTER XV

TAENIASIS

Introduction. Anatomy of the tapeworms. Development of the tapeworms. Biology of the tapeworms. *I. Infestation with Taenia solium.* Introduction. Symptomatology. Diagnosis. Treatment. Prophylaxis. *II. Infestation with Taenia saginata.* Introduction. Symptomatology. Diagnosis. Treatment. Prophylaxis. *III. Infestation with Diphyllobothrium latum.* Introduction. Symptomatology. Diagnosis. Treatment. Prophylaxis.

INTRODUCTION

Tapeworms have been recognized as intestinal parasites of man since the earliest days of medical history, and there never appears to have been any reasonable doubt as to their animal nature. There does appear, however, to have been a question in the minds of the ancients as to the "individuality of the tapeworm." That such was the case is obvious from the discussions found in the early literature regarding the morphological nature of these animals.

The ancient naturalists, recognizing the origin of the proglottids or segments of the worms that were frequently passed from the rectum of infected persons, maintained that tapeworms were made up of an aggregation of these separate segments. This view was held for some centuries, that is, until the discovery of the *head* of the large tapeworm of the dog, with its crown of hooks, by Tyson in 1683. Subsequently the heads of other tapeworms were obtained, as for example, that of the beef tapeworm, *Taenia saginata*, by Andry in 1700, and that of the fish tapeworm of man, *Diphyllobothrium latum*, by Bonnet in 1777. On the basis of these observations, the view came to be generally held that the tapeworm was a single independent animal which maintained its position in the alimentary canal by means of its head through which it also

received its nourishment. This view was strengthened by recognition of longitudinal canals, which were supposed to represent the intestine, extending throughout the length of the body and apparently having their origin in the organ or organs of attachment.

The first suggestion of an alternation of generations was set forth by Steenstrup in 1841, and this notion was further developed by numerous workers, among whom was Leuckart, and until recently was accepted by most authorities. According to this view, the tapeworm is not a single individual but is composed of several individuals represented by the segments or proglottids, and the scolex or head. The functions of these parts are quite separate and distinct, the proglottids acting in the rôle of sexual individuals and being concerned primarily in the perpetuation of the species, and the scolex or head, having to do not only with the maintenance of the worm in its position in the intestine, through the agency of its organs of attachment, but also producing the various individuals composing the worm itself. Thus it would appear, that the scolex would have to be present in the intestine before any of the proglottids could be found, and, though produced itself by sexual means, it would give rise to increase in the size of the worm by the formation of new segments by an asexual process. In consequence of this belief the development of the tapeworm was explained by an alternation of generations.

Some evidence to support the view set forth above was advanced when it was shown that not only the proglottids could separate from the strobila or tapeworm chain and live independently for a time at least, but that in some species of *Taeniae* the scolex as well was capable of separate existence. Subsequently when more complete information as to the development of the cysticercus or larval form was obtained, the truly independent nature of the scolex was recognized. This was shown to give rise to the strobila by a process of budding, the elements of the strobila—the proglottids—eventually becoming sexually-complete individuals. As a matter of fact it was thought that budding, or asexual reproduction occurred at

two stages in the life cycle, that is, in the formation of the scolex itself, from the preceding larval stage, and in the growth of the strobila by budding from the scolex.

More recent investigation has demonstrated the error of this conception and it is now recognized that the scolex is a part of the embryo or larva itself, and that in its development from this stage no process of asexual gemmation or budding is involved. Doubt has also been cast on the origin of the strobila by such a process.

At present the generally accepted belief is that the tapeworm represents a group or *colony* of zooids each unit of which is complete in itself as it possesses both male and female reproductive organs and is thus capable of perpetuating the species.

ANATOMY OF THE TAPEWORMS

With the exception of those tapeworms consisting of a single segment or proglottis, these animals are comprised of one scolex or head, a neck, and a larger or smaller number of segments or proglottids. The scolex carries the various kinds of organs by which the tapeworm fastens itself to the wall of the intestine and thus maintains its position in the gut. These organs of attachment are usually of a suctorial (acetabula) or fixation (hooklets) nature although in some species they have the character of a proboscis or tentacle-like structure.

The head of the tapeworm bears the suckers or hooks and the immediately posterior portion, which is usually unsegmented and flattened, is spoken of as the neck, while the proglottids appear back of this. The number of proglottids varies in different species from only a few to several thousand and these vary somewhat in appearance in different parts of the worm. Characteristically, the youngest segments, which are just posterior to the scolex, have their greatest diameter transversely, while the diameter of the older proglottids is greatest in the longitudinal direction. In becoming detached, the segments separate from the posterior end of the strobila

singly or in short chains, usually only after having reached maturity. Such free segments then continue to lead an independent existence for a considerable time.

The length of tapeworms is somewhat dependent on their age, but the adults of some species are recognized as only 0.5 to 1.0 millimeter in length, while others are known which attain a length of 10 meters or more.

The parenchyma makes up the chief tissue of the tapeworm body and consists of cells which lie in a non-cellular matrix containing fluid vacuoles. In the parenchyma are found a variety of structures such as calcareous corpuscles.

The muscular system of the segments consists of annular and longitudinal muscles together with dorso-ventral and transverse fibres.

The nervous system of the tapeworm arises in the scolex and extends longitudinally throughout the strobila, with certain variations in some species, and various ramifications within the individual proglottids.

The excretory system in these animals is subject to marked variation, but consists essentially of a series of collecting tubes, extending longitudinally throughout the body and supplied with transverse connections, and a network of vessels in the segments. Except for one genus, the tapeworms are hermaphroditic; the genitalia develop only in the proglottids, and the male organs appear before the female, as is usually the case with animals of this character. In certain genera there is a duplication of the genitalia in every proglottid.

DEVELOPMENT OF THE TAPEWORMS

In view of the fact that each segment of the worm possesses its own genitalia, having both the male and female organs fully developed, the following possibilities for fertilization must be recognized; (1) "self- or auto-fecundation; (2) self- or auto-copulation; (3) cross-copulation between proglottids of the same or different chains (of the same species); (4) cross-copu-

lation in the same proglottis in species with double genital pores. These various modes have actually been observed."

The eggs of the tapeworms possess shells, but there is as considerable variation in the shells as there is in their contents. A typical egg consists fundamentally of an egg-shell, ovum, and yolk cells. In the course of development the eggs undergo changes of size and shape and envelopes are developed around the embryo. In most species the embryonal development takes place while the eggs are still in the uterus although some species are known in which it takes place after the eggs have been deposited.

In the course of embryonic development two envelopes are formed. The inner one, surrounding the embryo itself, is known as the *embryophore* although it is sometimes erroneously spoken of as the egg-shell. The outer envelope is in close contact with the true egg-shell within which it remains when the embryo hatches out.

The embryo (the *oncosphere*), surrounded by the embryophore, is of various shapes but usually spheroid or ovoid and is characterized by the possession of six hooks. When this stage of development has been attained no further progress in the life cycle is possible, either within the proglottid, free in the intestinal canal of the host harbouring the adult tapeworm, or in the uterus of the evacuated proglottid. Thus the next step in development can only follow the passive entry of the oncospheres into a suitable host; this is frequently accomplished by way of water or food or by direct infection due to the coprophagous habits of many animals. In many instances infection takes place fortuitously through the ingestion of food or water contaminated with fecal material containing the embryos; in man it is sometimes accomplished through direct fecal contamination of the lips by soiled fingers.

Once entrance into a suitable host has been effected the oncosphere or embryo enters the next or larval stage of development. Occasionally this host is the same individual or

belongs to the same species as that in which the egg was liberated, but this is rarely the case. An example of this kind is found in the auto-infection of man with the larval form of the pork tapeworm, *Taenia solium*. From this point the transformation of the larva into the tapeworm is accomplished through the proliferation of segments or proglottids. These appear posterior to the scolex after it has become attached to the wall of the intestinal canal. The time necessary for the development of the complete strobila, or chain of segments, does not depend on the number of elements to be formed. This is shown by the fact that *Taenia echinococcus*, which generally has only three or four segments, takes ten to twelve weeks to complete its development, while only three or four weeks are required for the growth of the hundreds of proglottids composing the strobila of *Taenia solium*.

Determination of the amount of growth taking place daily has been made with fair accuracy in certain species, and it has been found that *Taenia saginata* increases in length approximately 7 cm. while in *Diphyllobothrium latum* the daily increase is about 8 cm.

BIOLOGY OF THE TAPEWORMS

The adult tapeworms infest the intestinal canal of vertebrates almost exclusively, and in some cases select definite portions of the gut for their residence. In some of the fishes the worms appear only in the stomach, while in sheep they have been found in the pancreas. When in the alimentary canal they are usually found in the small intestine, and when located in the large intestine they may be on the way to evacuation. In a few species they habitually fix themselves in the common bile duct.

Tapeworms are commonly regarded as inert animals but this is an erroneous notion as some of them are actually quite active. Not only do they exhibit local activity within the intestine, but they often migrate to the ducts communicating with the alimentary canal, to the stomach, and even at times to the

esophagus. Under abnormal conditions they may also invade other abdominal organs through routes temporarily opened-up between the intestine and such organs. In this manner penetration of the abdominal cavity, the urinary bladder, or the peritoneum may be accomplished.

The effects produced by infestation with tapeworms are diverse. The lesions resulting from such infection are most marked in the intestinal mucosa in the region of attachment and vary considerably with the mode of fixation. Elevation of the mucous membrane in "knob-like areas" is caused by the suckers, and atrophy or even complete destruction of the epithelial cells is often seen. In some species the worms bore into the openings of the glands of Lieberkühn and dilate the lumen to several times its normal size. Penetration deep into the submucosa frequently occurs, and at times the scolex may be found actually embedded in the musculature of the intestinal wall, or perhaps even protruding beyond into the abdominal cavity.

The nourishment of tapeworms living in the intestinal canal is obtained by absorption of nutritive material from the fluid contents of the gut. This process can take place throughout the entire length of the worm.

The natural duration of life of adult tapeworms is a variable matter. In some species it is only a relatively few days, while in others, and among these are included the species infesting man, it may last for years. When natural death occurs it is the result of alterations occurring in the scolex of the worm, such as degeneration of the organs of attachment, or even separation of the scolex from the strobila. It should be mentioned, however, that this event is not necessarily followed by the death of the parasite as in some species alterations take place in the anterior proglottids resulting in new organs of attachment.

Finally, multiple infestations may occur. Usually man is the host of but one tapeworm at a time but multiple infestations are not infrequent and furthermore infection with one

species does not apparently militate against infestation with another. Thus the various species are not mutually exclusive and infestations with *Taenia solium* and *Taenia saginata*, for example, may occur in the same individual.

Tapeworms are also found frequently associated with other intestinal parasites. Among these may be mentioned hook-worms, Ascaris, Trichuris, and Oxyuris.

I. INFESTATION WITH *TAENIA SOLIUM*

Introduction

The derivation of the name tapeworm is a matter of some dispute; the Greeks and Romans recognized them and in Latin they were at first called *taenia*, *tinea*, or *taeniola*, somewhat later *Lumbrici lati*, the *lati* being added to distinguish them from the *Lumbrici teretes*—the Ascaridae.

The first differentiation of *Taenia solium* from other tapeworms was made by Plater in 1602, when he distinguished it from *Taenia intestinalis* or *Diphyllobothrium latum*, as it is now known. The word *solium* had previously been used by Villanovanus to signify a belt or chain, although later writers, notably Andry, trace the origin of the word back to the Latin “solus” because it was thought that multiple infestations never occur in man. Leuckart believed *solium* was derived from the Syrian term meaning chain.

Invasion of man by this tapeworm is a chronic process with the adult parasite located characteristically in the alimentary canal. Only under abnormal conditions does the adult worm leave the intestine, that is, when unusual communications are established between the canal and contiguous organs. When such is the case the parasites may reach the abdominal cavity, may burrow into the peritoneum and cause abscesses, or may penetrate the urinary bladder.

Taenia solium is usually known as the “armed” or “measly pork” tapeworm. These names refer respectively to the fact that the scolex is armed with definite hooklets for attachment,

and that the larval stage in pork results in what is known as "measly pork." The larval stage also appears in other animals than the pig; dogs, sheep, the stag, cats, bears, monkeys, and wild boars, have been found infested, and in rare instances even man himself has been found to harbour the intermediate stage. From a practical standpoint however the only possible source of infection for man that is of any importance is the domestic pig. As might be anticipated this parasite is not observed in those peoples among whom the consumption of pork is forbidden by religious law, notably the Mohammedans and Jews.

The adult parasite. The average length of *Taenia solium* is 2 to 3 meters, although individuals 8 meters long have been reported. The head of the parasite is globular, about 1 mm. in diameter, with an apical rostellum armed with a double row of 25 to 50 hooks and 4 suckers. The rostellum is sometimes pigmented. The neck of the worm is fairly short and slender. Back of the neck the chain of proglottids begins, the anterior segments are much broader than long, at about a meter from the head they appear just about as long as broad and back of this the length is approximately twice the width. Each proglottis bears a small lateral genital pore, almost regularly alternating from the right to the left side of the chain. Within the segments the uterus is centrally located and consists of a medial stem with 5 to 10 thick dendritic branches on each side. The eggs are oval to spherical with a very thin and delicate egg-shell, while the shell of the embryo—the embryophore—is thick and radially striated. Within the embryophore the oncosphere with its six hooks is readily recognized.

In the adult stage the pork tapeworm is exclusively an inhabitant of the alimentary canal of man, where it maintains its position in the upper portion of the small intestine by means of its hooklets. A few gravid proglottids may appear, detached from the parasite, in the lower bowel but these are merely on the way to evacuation with the feces. Occasionally detached segments are brought up during vomiting.

Taenia solium is widespread geographically and human infestation parallels its occurrence in the domestic pig and the habit of eating pork raw or undercooked. In certain areas, notably in restricted districts of England, France, Germany, and Italy infestations with this parasite have been very common. It occurs rarely in Asia, Africa or in the East, because of the restriction of the dietary due to religious belief. In the United States infection with *Taenia solium* appears with a

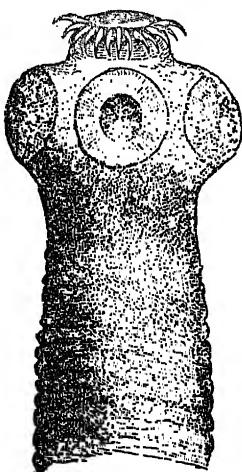


FIG. 18

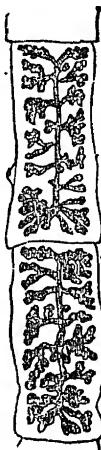


FIG. 19

FIG. 18. HEAD OF *TAENIA SOLIUM*. $\times 45$. AFTER FANTHAM, STEPHENS AND THEOBALD

FIG. 19. TWO MATURE PROGLOTTIDS OF *TAENIA SOLIUM* WITH FULLY DEVELOPED UTERUS. $\times 2$. AFTER FANTHAM, STEPHENS AND THEOBALD

rarity corresponding to the rare occurrence of the larval stage in the domestic pig.

Multiple infestations with the pork tapeworm are more frequent than with the beef tapeworm, *Taenia saginata*, but as a rule only one parasite is present in its human host.

The larval stage. The adult worms occur practically only in the human intestine, and the gravid segments are discharged

from this source and release the ripe embryos or oncospheres on disintegration. These are taken into the digestive tract of susceptible animals, which act as the intermediate host, and in which the larval or intermediate stage—known as *Cysticercus cellulosae*—appears. In the great majority of cases the pig is the animal infested with this stage, and becomes infected either by means of food or water containing the oncospheres, or by direct coprophagy.

After gaining entrance to the intermediate host the embryo loses its surrounding membrane through digestion, and once liberated bores through the intestinal wall to gain the blood stream and to be distributed throughout the animal body. Development of the cysticerci is usually in the musculature, although they may appear in almost any organ of the body, especially in the tongue, neck, and muscles of the shoulders. Having attained their ultimate destination, whatever it may be, the larvae encyst and appear as small ovoid vesicles filled with fluid. In this condition they are also known as bladder worms and at times are so numerous as to equal half the volume of the meat. Such infested pork is known as "measly pork" and constitutes the principal source from which infection is contracted by man.

When measly pork, or other meat in which *Cysticercus cellulosae* is present, is ingested by man—the definitive host—the wall of the cyst is dissolved by the gastric juice. The liberated cysticercus then passes into the small intestine and affixes itself to the gut wall by means of its hooklets after which development of proglottids commences. From this point the life cycle of the parasite is repeated.

Under some circumstances the cysticerci may form in man as the result of auto-infection due to reverse peristalsis or to oral contamination from hands soiled with feces containing the oncospheres. When human infestation with cysticerci does occur, the parasites may appear in almost any locality in the body, as in the brain, eye, muscles, heart, liver, lungs, or abdominal cavity. In addition to auto-infection, human beings

may also become infested through the introduction of the oncospheres into the stomach from water or vegetables—particularly in salads.

Symptomatology

The symptoms of taeniasis are generally more or less obscure and in some cases, especially in vigorous adults, there may be nothing definite. In other individuals, particularly in adults in a debilitated condition or in children, infestation with tape-worms may cause indigestion, anorexia, colic, and sometimes giddiness, headache, tinnitus and syncope. Other symptoms not infrequently exhibited are disorders of vision, salivation, nasal and anal pruritis and a sense of heaviness in the abdomen. At the same time there may be a feeling of lassitude in the limbs accompanied by pain. In some cases emaciation and more or less anemia may be observed. Occasionally a severe anemia is seen.

The symptoms following human infection with the larval stage of *Taenia solium*, i.e., *Cysticercus cellulosae*, are diverse and depend somewhat upon the location of the cysts.

When the cysticerci are in the cutaneous or muscular tissue, depression and a feeling of weakness in the lower limbs, abnormal sensations, sensory disturbances, inflammation of the sciatic nerve and numbness in the hands—which are painful when moved—are commonly noted. If located in the arm muscles, the cysticerci give rise to stiffness and difficulty in extending the arm. Located in the gluteal muscles they give rise to difficulty in defecation. When present in the temporal region headaches and neuralgic pains result. In some instances the cysts have become infected and occasionally suppurate.

If by chance the larvae come to rest in the eye their position may be varied. In many cases they appear in the region of the inner angle, where they produce a spherical protrusion but cause little trouble other than some irritation and difficulty in closing the eyelid. Suppuration of the cyst in this location may be attended with serious results. Cysticerci in the brain

are not uncommon and frequently give rise to cerebral diseases. If present in the brain they may be found in the dura and pia mater, choroid plexus, the medullary substance, ventricles, corpus striatum, corpora quadrigemina, pons, bulb, or medulla oblongata. Probably the most frequent location is in the ventricles or cortical substance. As a result of location in these areas very slight or very severe symptoms may appear. Localized pains and a degree of pressure result, together with psychical disturbances and epilepsy. Cysticerci in the ventricles are especially dangerous giving rise to headache, vomiting, vertigo and sleepiness, while there may be evidence of involvement of the hind-brain at the same time, consisting of pain and stiffness in the neck, vertigo, violent and persistent vomiting, retarded pulse and cerebellar ataxy. When the infestation is in the bulb paralysis of the cerebral nerves and respiratory disturbances are common. When located in the cerebral meninges cysticerci have the same effect as tumors.

A notable peculiarity of cerebral infestation is the alternation of periods of severe reaction and periods of apparently normal condition, and in this respect there is a simulated appearance of functional nervous affection. When located in the fourth ventricle the cysticerci frequently give rise to Brun's symptom, that is, sudden and violent cerebral symptoms following change of head-posture. In such cases the termination of the disease is often sudden due to heart failure.

Localization of the cysts at the base of the brain gives rise to hydrocephalus and cysticercus meningitis, accompanied by headaches, confusion of ideas, mental dullness, apathy, defects in speech and dementia.

Diagnosis

The diagnosis of taeniasis is usually accomplished by the identification of the eggs or proglottids of the worm in the feces through the examination of a watery emulsion of such material under low power magnification. It is much easier to overlook the segments of *Taenia solium* than those of *Taenia saginata*.

as the gravid segments of the pork tapeworm are passed with the feces instead of appearing singly and spontaneously between stools as is the case with *Taenia saginata*.

When gravid segments are obtained the characteristics of the uterus are well brought out by pressing the proglottid flat between two glass slides. By this procedure the uterus with its median stem and 5 to 10 thick dendritic branches on either side becomes easily visible. As a further aid in the identification of the proglottids of different species Isaacs (1) has suggested the injection of the canals with India ink. This is accomplished by introducing a fine hypodermic needle into the substance of the proglottid near the lateral pore and penetrating one of the diverticulae. Slight pressure on the plunger of the syringe then fills all the branches of the uterus with ink so that when such a segment is subsequently pressed between glass slides the details of the injected uterus become more clearly visible.

Recognition of the eggs of the tapeworm is also possible but identification requires a certain amount of familiarity with tapeworm ova and a degree of technical skill not usually possessed by anyone other than a trained helminthologist.

Treatment

In the treatment of tapeworm infestation the worm must be first stupefied and subsequently expelled through the administration of purgatives.

In connection with the treatment certain precautions with reference to the diet should be observed. Some clinicians recommend that the patient fast for a period of 24 hours previous to the administration of the anthelmintic while others consider that the omission of the evening meal the day before the treatment is sufficient. Generally several small doses of a purge followed by an enema just before the taeniafuge will serve to materially clear the colon and allow the worm an unobstructed passage.

Other clinicians recommend administration of the remedy

and the purgative together in the morning on an empty stomach, although a cup of tea or coffee without milk may be allowed a half hour before the treatment. After the taeniafuge has been administered the patient should remain in bed and on defecation should pass the dejecta into a vessel of warm water in order to prevent contraction and breakage of the strobila.

Kirne (2) and others have recommended the injection of morphia into the parasite when the first proglottids are extruded from the rectum. At the same time the patient should resist the desire to defecate as long as possible as in this way the worm may be expelled in its entirety.

Whatever procedure is followed, if the head of the worm is not obtained no further treatment is indicated until the lapse of 10 to 14 weeks, or until definite evidence is obtained that the parasite still remains in the intestine. The reason for this is that the head may be passed unnoticed later, or it may be digested, so that there may be no new growth of the parasite, although the treatment has not been apparently wholly successful.

The taeniafuges usually employed are ethereal extract of male fern, pomegranate bark, or pumpkin seeds. Brumpt (3) directs that these anthelminitics be used in the following manner:

1. Pomegranate bark. Of the fresh bark 50 to 60 grams are macerated in water and made up to a volume of 750 cc., allow to stand about 12 hours and then boil the infusion until reduced about one-fourth. Add a little aromatic syrup before administration. One hour after the dose has been given, about 40 grams of castor oil is prescribed as the purgative.

Children take half this dose.

2. Ethereal extract of male fern (Oleoresin of male fern). Sixteen capsules of male fern, as prepared by the pharmacist, are given. The dosage is two capsules every ten minutes. In all about 8 grams of male fern should be given an adult, but not more than 2 to 4 grams to a child. Following this a non-oily

purgative should be given. It is recommended that the purge should be non-oily, as oil is believed to increase the risk of poisoning the patient by the male fern.

3. Pumpkin seed. This is one of the best remedies. As the active principle is most abundant in the cortex of the seeds the whole seed should be used. These are ground in a mortar with the addition of a little honey, the resulting paste is palatable and is taken readily by children. The dose is 30 to 50 grams according to age, and is followed in about an hour by a dose of castor oil or other purgative.

Recently the duodenal tube has been quite successfully employed in the treatment of taeniasis. The procedure, as followed by Schneider (4) is to give the patient a cathartic in the evening and after introduction of the tube next morning, on an empty stomach, to inject one-half of an infusion of senna (5 grams in 50 grams of water), fifteen minutes later the rest of the dose is given, but with the addition of 2 grams of extract of male fern and 4 grams of extract of pomegranate bark. As a rule the worm is expelled whole within about two hours. Following this method of treatment Schneider (4) and Klein (5) report expulsion of the worms in their entirety in 13 of 17 and 12 of 16 cases respectively. In those instances where this method of treatment was not successful, the failure was attributed to rolling up of the tube or inadequate dosage.

Besides the taeniafuges mentioned above, other preparations have been employed, such as turpentine, in doses of 20 minims, repeated three times during the day; kusso, in 2 drachm quantities; kamala, in the amount of one drachm; santonin; or thymol. Naphthaline in two grain doses has been used for children with considerable success.

Prophylaxis

Prevention of infection rests primarily on the avoidance of raw or undercooked pork and its products. This means ultimately thorough cooking so as to make certain that any encysted larvae present will be killed. Additional safeguards

of health involve the proper disposal of human feces so as to remove the possibility of infection in the hog through contaminated water or food. Finally, inspection of all carcasses at the time of slaughter may be of some assistance in detecting infected meat. Routine inspection cannot be relied on too much however, as such examination is necessarily limited to the heart and the visible portions of the muscles, particularly the muscles of mastication. Obviously many cysts may escape detection under these circumstances. Cold storage of meat cannot be depended to kill the cysticerci as they are quite resistant to freezing. This is quite contrary to experience with the larvae of the beef tapeworm.

Persons harbouring adult tapeworms should always receive treatment and be warned against the danger of auto-infection from vomiting or from contamination of the lips with soiled fingers as subsequent development of the cysticerci in the tissues of the body may result. As has been pointed out this infection is far more dangerous to man than intestinal infestation with the adult worms.

II. HUMAN INFESTATION WITH *TAENIA SAGINATA*

Introduction

The first description of *Taenia saginata*—the unarmed or beef tapeworm—was presented by Goeze, but his differentiation of this species from *Taenia solium* was over-looked, until attention was again called to their differences by Kuchenmeister in 1852. Except for restricted areas, in which some other species is found more frequently, *Taenia saginata* is the most common tapeworm occurring in man.

Geographically, the parasite is widespread; in the East it has been recognized for centuries and it occurs throughout North and South America, Europe and Africa. In fact, the appearance of the worm parallels the distribution of cattle as it is in these animals that the parasite generally passes the larval or intermediate stage.

Infection of the human host by this tapeworm is in the nature of a chronic disease, with the adult parasite located exclusively in the alimentary canal.

For a long time after differentiation of the adult worms from other species the intermediate stage of the parasite was unknown, nor was the host of the intermediate stage recognized. Certain facts indicated that the ox might serve in this capacity, however. For example, it was not infrequently observed by clinicians that children, for whom scraped raw beef was prescribed often became infested with *Taenia saginata*. It was also noted that *Taenia saginata* was frequently found infesting persons accustomed to eating beef but forbidden by religious law to eat pork. And finally, it was observed that *Taenia saginata* was most often found infecting certain nationalities among whom raw beef was habitually consumed. Such a group was represented by the Abyssinians.

Taken together, the facts cited above seemed to point to the consumption of raw or undercooked beef as the probable source of human infection, and inspired the crucial experiments that settled this point.

In 1861 Leuckart fed the proglottids of the adult *Taenia saginata* to calves in order to discover, if possible, whether such material could give rise to an infection in these animals, and if so, whether an intermediate stage or cysticercus form occurred in their bodies. The experiment was successful; a larval stage was observed as occurring in various locations in the calves, and the name *Cysticercus bovis* was given to these encysted larvae. Subsequently this feeding test was repeated by numerous workers among whom may be mentioned Mosler (1863), Gerlach (1870), and Masse and Pourquier (1876).

Following the recognition of the intermediate stage in the flesh of cattle, the crucial test of producing the adult parasite in man through feeding beef containing the encysted larvae was undertaken. In 1869 Oliver in India, and in 1877 Perroncito, in Italy, among others, reported the development of an adult tapeworm in the human subject as the result of ingesting

Cysticercus bovis. Thus our knowledge of the complete life cycle of this parasite was completed.

In contrast to the intermediate stage of *Taenia solium* which occurs in many animals, this stage of *Taenia saginata* almost never appears in other animals than the ox, under natural conditions. Of the great number of attempts made to artificially infect monkeys, rabbits, sheep, dogs, cats and pigs almost none have been successful. To all intents and pur-



FIG. 20

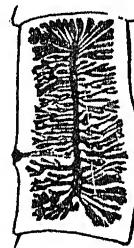


FIG. 21

FIG. 20. HEAD OF *TAENIA SAGINATA*. $\times 8$. AFTER FANTHAM, STEPHENS AND THEOBALD

FIG. 21. MATURE SEGMENT OF *TAENIA SAGINATA* WITH DISTENDED UTERUS. $\times 2$. AFTER FANTHAM, STEPHENS AND THEOBALD

poses then, man and the ox are the only animals concerned in the perpetuation of this species of parasite.

The adult parasite. *Taenia saginata* lives exclusively in the small intestine of man where it attains a variable length—from 4 to 10 meters as a rule—the chain or strobila consisting of hundreds and at times more than 1,000 segments. The head is pyriform, 1 to 2 mm. in diameter, has no rostellum or hooklets, but is equipped with an apical depression and 4 suckers. The neck is moderately long and slender, while the anterior

proglottids are broader than long, but gradually the ratio of the diameters changes until the segments near the posterior end of the strobila are considerably longer than broad. When mature the proglottids approach the shape of a pumpkin seed and when gravid readily detach themselves from the chain and pass out of the body by their own efforts, rarely with the feces. It is because of their possession of the power of independent motility that the proglottids are so often found free in the underclothing or in the bed of a person harbouring the parasite.

The genital pore is single in *Taenia saginata* as in *Taenia solium*, and alternates irregularly from side to side in successive segments. It opens to the exterior on the lateral margin.

The morphology of the uterus in gravid segments, of *Taenia saginata* is quite characteristic and also in contrast to its appearance in the pork tapeworm. The median stem is the same in both cases, but the branches number 15 to 30 on each side in the case of *Taenia saginata*, are dichotomous, and each branch in turn subdivides into other branches.

The eggs—more accurately the embryophores—are ovoid or nearly spherical, with a thick, radially striated shell which is transparent. Through this shell the six-hooked embryo or onchosphere is plainly visible.

Taenia saginata commonly lives only in the small intestine in its human host, where it attaches itself to the mucosa by means of the sucking apparatus. Stieda (9) has reported this parasite as found in the pancreas, but this is extremely unusual.

Ordinarily man harbours only one parasite at a time although multiple infestations may rarely occur.

The larval stage. As man is almost exclusively the host of the adult tapeworm, the gravid segments from the human intestine are practically the only source from which the ripe embryos or oncospheres can be liberated. To continue the life cycle these must gain entrance to the alimentary canal of an animal capable of acting as host for the larval or intermediate stage. As a rule, this means that they must be ingested by either man or a representative of the bovine species. In

the vast majority of cases the intermediate stage develops in the ox or some other ungulate, although the occurrence of the intermediate stage in man has been reported. In these cases, however, there may be room for some doubt as to the correctness of the identification.

When the eggs happen to gain entrance to the digestive tract of cattle or other susceptible animals, the six-hooked embryos escape from their shells as these are digested, and migrate into the musculature of the new host. Here they encyst in the intermuscular connective tissue exhibiting some predilection for the muscles of mastication.

In the encysted form the embryos develop into typical bladderworms, and are called *Cysticercus bovis*. At this age the head and neck are invaginated and appear as a yellowish spot showing through the wall of the cyst or bladder on one side. Such infested beef is known as "measly beef" and is the origin of practically all human infections. A striking illustration of this fact is found among the inhabitants of Abyssinia where the Mohammedans, who are prevented from eating raw meat by religious law, are almost entirely free from tapeworms, while the balance of the population is heavily infested.

When the embryo of *Taenia saginata* has encysted in the musculature of an ungulate no further development is possible until such meat is eaten by man, and unless such measly meat is so eaten the parasite may be thought of as having reached a "blind alley" as the life cycle cannot be completed otherwise.

After infested meat is consumed by a human being, the wall of the cyst is digested away in the stomach after which the live cysticercus passes into the small intestine, where it becomes attached to the mucosa and the formation of proglottids, just back of the scolex, in the neck region, begins. As the new segments are formed they are pushed further and further back from the head, growth in size continues and gradually they approach sexual maturity. When this is attained auto-fertilization takes place and the uterus is soon filled with thousands of eggs. From this point the life cycle is repeated.

The life of cysticerci in the muscles of cattle is of variable duration and according to Ransom (10) they usually undergo degeneration inside of a year although they may remain alive for several years. Presumably, the location of the cyst has something to do with the length of life of the embryo as it has been found that when located in the heart they undergo degeneration much quicker than when located in some of the voluntary muscles.

Symptomatology

In many cases the individual harbouring the tapeworm does not suspect that he is infested, as his general condition is quite normal, and suspicion is aroused only when segments commence to be discharged. On the other hand people sometimes develop the idea that they are harbouring a tapeworm when they are not and it is extremely difficult to overcome this impression. To such imaginary taenias Kuchenmeister has given the name *Taenia imaginata*.

In some cases indigestion, nausea, vomiting and derangements of appetite occur. A sensation of pressure may be felt in the abdomen localized constantly on one side or shifting from side to side, now in the region of the epigastrium and now at the umbilicus. Colicky pains often occur and there may be either constipation or diarrhea. Bilious attacks are frequent, accompanied by colic, icterus, pigmented urine, nosebleed, enlargement of the liver and spleen, ascites and edema of the legs.

The effects on the nervous system are varied and give rise to numerous symptoms among which may be mentioned epileptiform attacks, headache, hysteria, chorea, convulsions, paralysis of various sorts, pseudomeningitis, aphonia, dyspnea and cardiac disturbances. Disturbances of vision are not infrequent. Nasal and anal pruritis is often experienced.

In adults in good health the effect of tapeworm infestation may be negligible, but in debilitated or nervous individuals and in children, the effects may be marked. In some such persons

the chief harm from the worm may be the loss of a considerable amount of nourishment. But there are patients who appear to develop severe anemia as the result of harbouring the parasite. Whether this anemia is due to lack of sufficient nourishment or to the production of toxic substances by the worm, which are absorbed from the intestine by the host, is not easily established. In the case of infection with another tapeworm—*Diphyllobothrium latum*—it is well known that the danger of the infection is due to the toxic substances produced by the parasite which give rise to intense anemia.

Fortunately, infestation of man by the intermediate stage—*Cysticercus bovis*—practically never occurs, and in this respect this parasite differs distinctly from *Taenia solium*.

Diagnosis

Recognition of infestation with *Taenia saginata* is usually accomplished through the observation that segments of the worm spontaneously escape from the rectum, or by identification of proglottids or eggs occurring in the feces. It is also important to note that the segments as eliminated occur singly in the case of *Taenia saginata*, while there are usually several segments linked together when *Taenia solium* is the source.

An excellent method for the demonstration of the characteristics of the uterus has been suggested by Isaacs (11) and consists of injecting India ink into one of the branches of this organ by means of a hypodermic syringe and a fine needle. In this manner all the ramifications of the uterus are made clearly visible when the segment is pressed between glass slides. If the proglottid came from *Taenia saginata* it will be seen that the uterus consists of a median stem with 15 to 30, slender, dichotomous branches on either side, and that these branches in turn have ramifications.

Recognition of the egg is accomplished by identifying the hexacanth embryo enclosed within its thick, radially striated, embryonal shell.

Treatment

The removal of *Taenia saginata* from the human intestine is much more difficult than the removal of *Taenia solium*. The principle of first stupefying the worm and then bringing about its expulsion through the agency of a purge is the same in both cases. It is necessary to guard against too radical treatment in the case of elderly persons, persons weakened by disease or operations, in pregnancy and in patients suffering from gastric or intestinal growths, as well as those suffering from heart disease. Treatment under any of these conditions should be of the mildest sort that will result in elimination of the parasite.

In this instance, as in treatment for the removal of other tapeworms, some preparation is necessary before the administration of the taenifuge. This consists in fasting during the day of the treatment, and the removal of as much material from the bowel as possible before the treatment begins. Repeated small doses of a laxative during the day preceding treatment and a simple enema just before treatment serve to bring about the desired result.

On the day the taenifuge is to be given the patient should be allowed nothing more than a cup of black coffee or tea, without cream or sugar, about half an hour before the drug is taken.

The remedies advertised as vermifuges are almost without number and many of them have no virtue whatever. The preparations that have been used with uniform success and that are recognized as effective are pomegranate bark, pumpkin seed paste, and extract of male fern. Directions for the preparations of these materials have been given under the treatment of *Taenia solium* to which reference should be made for details. Repetition of the warning against overdosage with extract of male fern is not out of place however. When more than 10 to 12 grams of this extract are given very severe toxic symptoms may ensue. These are best obviated by administration of a purge about half an hour after the extract has been given so that it will not remain in the intestine longer than necessary.

This purge should be of saline as oils promote absorption of the drug.

In the treatment of children the pumpkin seed preparation or kamala is preferable to extract of male fern.

Potassium bromide, ether, napthalin, strontium lactate, glycerine, and croton-choral are ineffective and should not be accepted as vermifuges.

After the worm has been expelled careful search should be made for the head, as without its removal further growth is probable. In case the scolex is not found no further treatment is indicated for a matter of several weeks or until it is definitely established that growth has recommenced.

Prophylaxis

The prevention of infection in man rests fundamentally on thorough cooking of all beef before it is eaten as it has been shown that a temperature of 48°C. quickly destroys the cysts. Cold storage of beef also offers a measure of protection as the cysticerci do not survive more than a week in beef that is frozen. The length of time intervening between slaughter of the beef and its consumption as food is also a factor influencing its infectivity as *Cysticercus bovis* does not survive the death of its host more than three or four weeks.

The proper disposal of excreta from persons harbouring the parasite is important in controlling the spread of the disease. As such an individual may discharge several hundred proglottids per month, each of which is turgid with eggs, it is essential that they be destroyed. If this is not done it is obvious that they may be distributed by such agencies as rain water, flies, or other insects and eventually reach the drinking water or food of cattle and give rise to further bovine infection.

III. HUMAN INFESTATION WITH DIPHYLLOBOTRIUM LATUM

Introduction

Diphyllobothrium latum is commonly called the fish or broad tapeworm of man and belongs to the family of the Dibothrio-

cephalidae; rather than to the family of the Taeniidae of which *Taenia solium* and *Taenia saginata* are members. It is characterized by having a head with two grooves or suckers.

In the literature it has been described under a variety of names among which may be mentioned *Dibolhriocephalus latus*, *Bothriocephalus latissimus*, *Bothriocephalus latus*, *Dibothrium latum*, *Taenia dentata* and *Taenia lata*.

The geographical distribution of *Diphyllobothrium latum* is world wide but it is of prime importance to man only in those countries where fresh-water fish is extensively eaten, particularly in those regions where it is eaten after little cooking or in the raw state, as in Russia and Japan. In Europe the parasite occurs in practically all countries, while in the United States there are endemic areas of infection, especially in the region about the Great Lakes, where human infestation is much more common than was formerly appreciated.

For many years after recognition of the adult form of this parasite and its differentiation from other species of tape-worms, the life cycle was not understood. It was not until 1883 that Braun demonstrated its developmental stages in fish although the complete life cycle was not worked out until 1917 by Janicki and Rosen (15).

In man *Diphyllobothrium latum* lives in the small intestine where one or many of the parasites may be found at a time and from which the eggs are evacuated with the feces. After deposition of the egg further development takes place necessarily in water where the oncospheres or embryos are liberated and for a time lead a free living existence. Unless these embryos then succeed in gaining entrance into the intermediate host, which is a crustacean—Cyclops—they remain alive only for a limited time. On the other hand if they do invade an intermediate host their development continues, and when these infected copepods are subsequently ingested by one or another species of fresh-water fish, the larvae penetrate the intestine and develop into plerocercoid larvae in the muscles. The ingestion of such infested fish by man results in the attachment

of the head of the parasite to the intestinal wall and the subsequent development of proglottids. At this point the life cycle of the parasite has been completed.

The adult parasite. *Diphyllobothrium latum* is a large tapeworm, often attaining a length of 6 to 30 feet, the strobila consisting of 3000 to 4000 proglottids. In exceptional instances a length of 50 to 60 feet has been reported. The transverse diameter of the segments is greater than the longitudinal and it is only in the terminal proglottids that the length is greater than the width. The worm is grayish-red in color.

The head or scolex of the parasite is almond-shaped and the dorso-ventral axis is greater than the transverse. There are no hooklets or organs of attachment other than two grooves or suckers, known as bothridia, one ventral, the other dorsal. The length of the neck varies according to the degree of contraction and it is very thin. In this, as in other tapeworms, growth takes place at the head-end and the oldest proglottids are those most removed from the scolex. The outstanding feature of the proglottids in this species is that they are much broader than long. This is true of the segments throughout the chain but is not so markedly noticeable in those that are oldest. The accumulation of eggs in the uterus frequently gives rise to the appearance of a dark area in about the center of the segment.

In this species as in the taenias, both male and female reproductive apparatus is present in each segment and the appearance of the organs is quite distinct and characteristic. The testes are numerous, and dorsally located, the vas deferens forming transverse loops and in the anterior portion gives rise to a seminal vesicle before entering the cirrus pouch. The ovary is bilobed and has been likened to the wings of a butterfly in shape. It is ventrally located and provided with an oviduct which empties into the cirrus. As a consequence of this arrangement of the genitalia the fertilization of the eggs is accomplished before they are expelled from the body of the worm. As expulsion takes place little by little the proglottids undergo a progressive

diminution in size until there are no more eggs left in the uterus after which the segments separate from the strobila and are eliminated as debris in the fecal material in a form difficult to identify.

The genital orifice in *Diphyllobothrium latum* is ventrally located near the middle of each proglottid instead of in the lateral margin as in the taenias.

The larval stage. For the continuation of the species in *Diphyllobothrium latum* a certain amount of development is essential in two different intermediate hosts. The first host is a crustacean copepod, the second a fresh-water fish, and the final, or definitive host, is man.

In contrast to *Taenia solium* and *Taenia saginata* the eggs of *Diphyllobothrium latum* are habitually expelled from the proglottids into the intestinal canal of the definitive host from which they escape in the feces. They are large, ovoid and surrounded with a brownish shell within which the hexacanth embryo, or oncosphere, forms in a few days after evacuation, providing the temperature of the surrounding medium is between 30° and 35°C. Between 10 to 15 days are generally required for its development. The oncosphere is enclosed within an embryonal membrane bearing cilia by means of which it is enabled to swim about, although the embryos sometimes leave their ciliated shells and creep about at the bottom of the body of water in which they have been released. At this point further development of the larva depends upon its ingestion by a crustacean copepod which acts in the rôle of first intermediate host. If this happens to take place the next step in the completion of the life cycle is possible, that is, a procercoid larva—a fully developed larva—is formed in about two weeks. Subsequently, ingestion of these infected copepods by such fresh-water fish as pike, miller's thumb, and perch permits the development of the next stage of the parasite—the plerocercoid larva. These larvae appear not only in the intestine of the fish, but penetrating the gut wall, develop also in the liver, spleen, genital glands and musculature.

The completion of the life cycle necessitates that infested fish be eaten by a susceptible animal such as a dog, cat or man. If this occurs the encysted larvae are freed in the stomach through the action of the digestive juices, after which they pass into the small intestine, where they become attached and the life cycle begins over again.

Symptomatology

The disturbances produced in man by *Diphyllobothrium latum* may be of little consequence or may be most serious. If the symptoms are those of simple gastric or nervous disorders they may not attract much attention. If they are of a toxic character they may be grave as it is well recognized that this species is the source of blood-destroying substances that may give rise to profound anemia.

Reyher (16) first called attention to the fact that this parasite may cause a severe, progressive and not infrequently fatal anemia, and he also showed that quick relief followed expulsion of the worm. In the literature many cases of infestation with *Diphyllobothrium latum* have been reported which presented the classic picture of pernicious anemia, and here references may be made to the reports of Schapiro (17), Podwissotzky (18), Pariser (19), Schauman and Tallqvist (20) and Meyer (21) as examples. An excellent review of this subject has been made by Fedorov (22).

It seems probable that a certain number of cases of bothriocephalus anemia may have been confused with pernicious anemia and an erroneous diagnosis established. Those suffering from anemia due to infestation with the parasite present extreme pallor, weakness, cardiac disturbances, edema and ocular hemorrhages. The gastro-intestinal disturbances consist of vomiting and diarrhea. Histological examinations demonstrate the same pathological lesions in both cases.

The blood changes are most marked and of primary interest. Reduction of red blood cells is usually to 2,000,000 and sometimes to 500,000 and many nucleated red cells appear. There

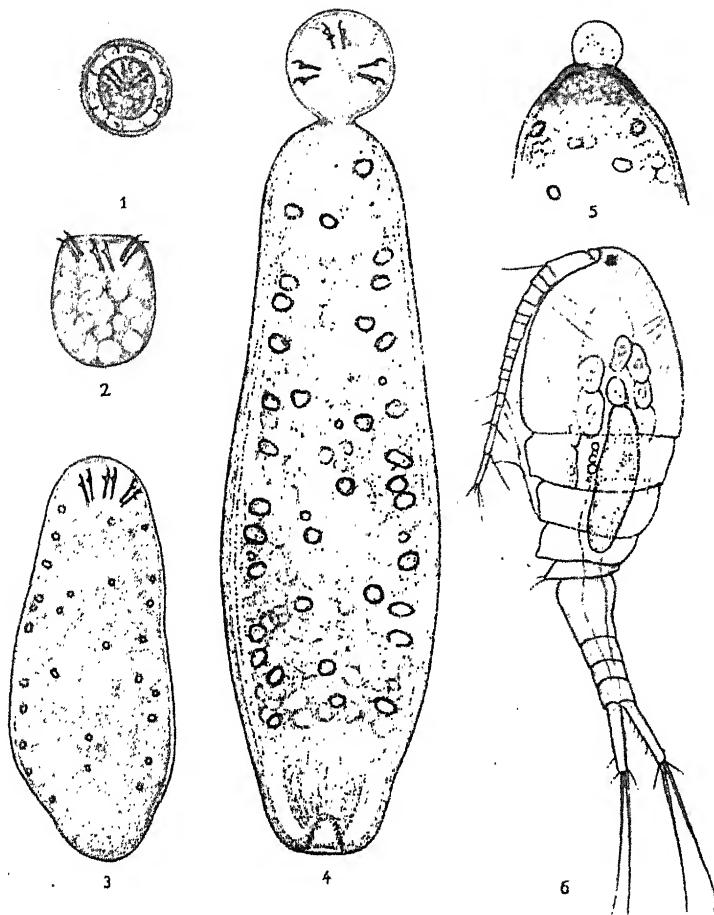
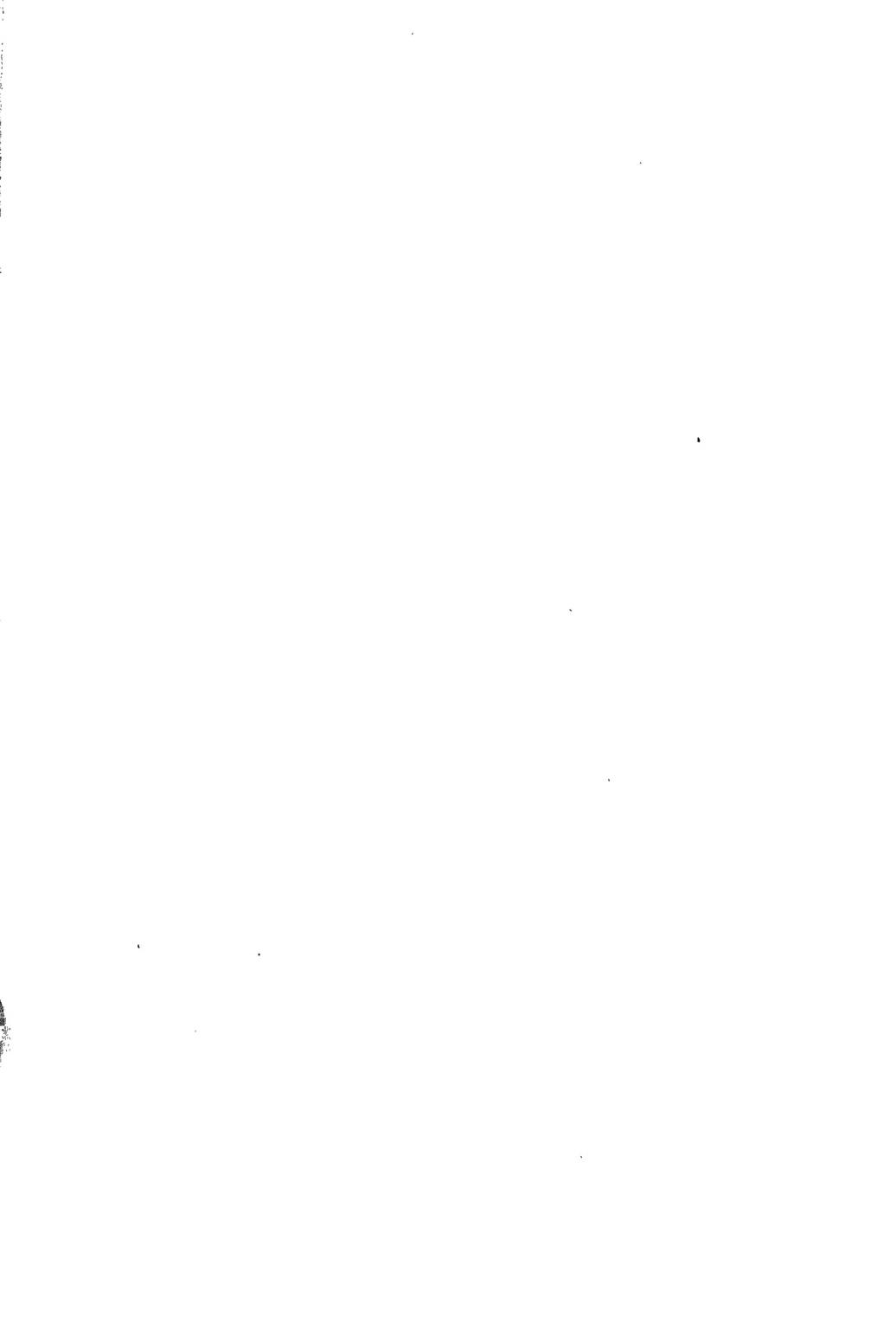


FIG. 22. EVOLUTIONARY CYCLE OF *DIPHYLLOBOTRIUM LATUM*

(1), Ciliated oncosphere, $\times 280$; (2), oncosphere after having lost its ciliated envelope, in the copepod, $\times 280$; (3), the same oncosphere after further growth, $\times 280$; (4), procercoid larva after 20 days growth in the body cavity of cyclops, $\times 280$; (5), anterior extremity of the procercoid larva, $\times 280$; (6), *Cyclops strennus* containing a procercoid larva, $\times 60$. After Janicki and Rosen.



is less tendency for the red cells to appear in clumps than in normal blood and at the same time there is a diminution of leucocytes.

Just how the lesions brought about by the parasites are to be explained is not clear, although the matter has been the subject of numerous investigations. One suggestion has been that *Diphyllobothrium latum* produces a toxin or poison of some sort which is absorbed from the intestine and has a direct destructive action upon the blood and may also have some effect on the blood-forming organs. Thus Schauman (20) fed dogs and rabbits portions of the parasite and also injected them with extracts of the worm. The rabbits never showed any effects, but the dogs developed all the signs of a severe anemia about 15 days after the material was given. Schauman and Tallqvist, also demonstrated that the segments of the worm possessed a hemolytic substance of a lipoidal character. On the whole, however, it cannot be said that the cause of bothriocephalus anemia has been established as no explanation for its frequency in some areas, as in Russia and around the Baltic Sea, and its rarity in other regions where the parasite is common, as in Switzerland is apparent at the present time.

Diagnosis

The recognition of the eggs of *Diphyllobothrium latum* in the feces is the usual method of making a diagnosis, although the clinical observations may be sufficiently striking to suggest the presence of an intestinal parasite. It is improbable that recognizable portions of the worm will be obtained until after administration of a vermifuge. When these are found identification is easy as *Diphyllobothrium latum* is quite distinct from the other intestinal parasites of man.

Treatment

No special treatment is indicated in cases of infestation with this tapeworm other than the administration of a drug that will stupefy the parasite in the intestine followed by a purge

that will bring about its expulsion. For the details of such procedures the methods of treatment outlined in the discussion of *Taenia solium* and *Taenia saginata* should be consulted.

Prophylaxis

The only source of infection for man is found in raw or undercooked fish and thorough cooking of such meat is all that is necessary. In those areas where the practice of eating raw fish is common, it should be discouraged as should also be the consumption of caviar made of the eggs of fish that are known to act as the intermediate host for the parasite.

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CHAPTER XVI¹

OTHER PARASITES OF MAN ACQUIRED THROUGH FOOD

Introduction. I. Parasites having a stage which is immediately infective when passed in the stool. II. Helminths only becoming infective after development in the environment. III. Helminthic parasites having the larval stage transmitted by an arthropod. IV. Parasites transmitted by food bearing the larvae.

Human infestation with the parasites to be considered in this chapter is brought about in a variety of ways. Some of the parasites infect man as the result of unconscious ingestion of fecal material containing the infective stage of the organism. Others gain entrance to their human host through his ingestion of a food substance, in or upon which the infective stage of the parasite occurs. To a greater or lesser degree it is thus clear that the methods of transmission of these parasites have a relationship to food infection and may therefore be appropriately discussed under the captions given below:

- I. Parasites of man, 'having in their life histories a stage which is infective when passed in the stool, infection with which is acquired through direct fecal contamination of food or of the lips.'
- II. Helminthic parasites of man only becoming infective after undergoing a certain amount of development in the environment, infection with which is acquired through indirect fecal contamination of food, or of the lips.
- III. Helminthic parasites of man, infection with which is acquired through the ingestion of an arthropod intermediate host, which contains the larval stage.
- IV. Helminthic parasites of man, infection with which is acquired through the ingestion of some food substance, in or upon which the larvae have encysted.

The means by which human infection is acquired necessarily overlap to a certain extent. It is believed, however, that discussion of the material to be considered, under the four divisions indicated above, is justified. Such a presentation, it is

¹By Norman R. Stoll.

hoped, will emphasize not only the growing complexity of the life cycle of the species through succeeding topics, but will also be of assistance in the differentiation of methods for the prevention of infection.

Four tables included in the text recapitulate the material taken up in detail under each of the headings. These tables include not only those parasites whose life histories and thus modes of infection and prevention are known, but also some of the related but less common forms encountered in man, having presumably similar modes of infestation.

I. PARASITES OF MAN, HAVING IN THEIR LIFE HISTORIES A STAGE WHICH IS INFECTIVE WHEN PASSED IN THE STOOL, INFECTION WITH WHICH IS ACQUIRED THROUGH DIRECT FECAL CONTAMINATION OF FOOD OR OF THE LIPS (TABLE III)

Strictly speaking, infection with the parasites here considered, is not so much a problem of food borne infection as of direct fecal contamination of the fingers and lips. The distinction must obviously not be too finely drawn. Organisms which may reach the mouth directly from fingers are quite as likely as well to arrive on many kinds of food contaminated by soiled fingers. What may be thought of as hygienic precautions are thus primarily of importance in prophylaxis.

Hymenolepis nana, the dwarf tapeworm, is probably of cosmopolitan distribution and has come to be considered as the most common human tapeworm in the United States, especially in children. It is morphologically indistinguishable from a species found in rats and mice, *Hymenolepis fraterna* (*Hymenolepis murina*). Joyeux (1) has maintained that the rodent and human strains are physiologically distinct and not cross-infective, but the work of Woodland (2) indicates that the ova of *Hymenolepis nana* from infected children sometimes develop in mice. From the hygienic standpoint, these rodents should therefore be considered as a possible reservoir, although not a usual one, of human infection. The embryos are set free in the intestine, bore into the villi and there pass the cysticercoid

TABLE III
Parasites of man, having a stage which is infective when passed in the stool, infection with which is acquired through direct fecal contamination of food or of the lips

GROUP	NAME OF PARASITE	OTHER NAMES SAME ORGANISM	RESERVOR HOSTS	PART OF HUMAN BODY PARASITIZED	RELATED FORMS WITH PROBABLY SIMILAR METHODS OF INFECTION	
					GEOPGRAPHICAL DISTRIBUTION	
Trematodes	None			Larvae in villi, small intestine; adults in lumen of same	Probably cosmopolitan	
	<i>Hymenolepis nana</i>	Dwarf tape-worm	Man (rats, mice?)	Liver; lungs, kidneys and erratic locations	Cosmopolitan	Multiceps sp.
	<i>Echinococcus granulosus</i>	Hydatid	Dogs	Liver, etc.	Europe (Tyrol)	Adults in carnivores
Cestodes	<i>Echinococcus multilocularis</i>	Beef tapeworm	Dogs	Muscles; also erratic locations	Probably cosmopolitan	
	<i>Cysticercus bovis</i>	larval	Man	As above		
	<i>Cysticercus cellulosae</i>	Pork tapeworm	Man			
Nematodes	<i>Enterobius vermicularis</i>	Seat or pin-worm	Man	Young in small intestine; adults in or near appendix; gravid females in rectum	Cosmopolitan	

stage, later emerging and becoming adult. The adults are small, 5 to 45 mm. in length and consist of 100 to 200 or more proglottids. Infestations with large numbers of worms may occur and then loss of appetite, diarrhea and nervous disturbances may result.

Diagnosis is by fecal examination. The eggs are oval or globular with two distinct membranes, the inner membrane having filiform projections at each pole. These eggs should not be confused with those of another species of the same genus, namely, *Hymenolepis diminuta*. Oil of chenopodium is said to be effective against *Hymenolepis nana* but not against other intestinal cestodes.

Enterobius (Oxyuris) vermicularis, the common pin or seat worm, is a strict human parasite, cosmopolitan in distribution, and primarily occurs in man as an infection of children. When the ova are swallowed the young hatch in the small intestine, and the adults are later found in or near the appendix and beyond, in the large intestine. Their association with appendicitis is probably small or negligible. Besides anal itching, the parasites may produce nervous symptoms of varying degree.

The gravid female worms migrate down into the rectum, from where they are often carried out with the feces. It is probably these worms, found in the feces without preceding vermifuge, which are occasionally reported by the laity as human hookworms in the stool. At times the female worms may also be found free in the underclothing or in the bed, having wandered from the anus. Under such conditions they may cause intense itching in the moist perineal region, and in the course of such migrations may wander into other natural openings such as the vagina. Scratching of the body in these regions that are open to infection undoubtedly is a method by which the fingers become contaminated with the ova. These ova contain fully infective embryos within a few hours after discharge.

In making a microscopic examination of feces, the preparation should be secured from the outside of a fecal mass, if pos-

sible after a formed movement. The egg is rather small, flattened on one side, contains the embryo when voided and is quite distinctive in appearance. Various methods of treatment have been employed in this condition, and a combination of several is often useful. Because of their location in the lower portion of the intestinal tract treatment should be by drugs such as thymol, male fern, or oil of chenopodium, which are not readily absorbed from the intestine.



FIG. 23



FIG. 24

FIG. 23. FULL GROWN TAENIA ECHINOCOCCUS. $\times 12$. AFTER ZIEGLER
FIG. 24. ECHINOCOCCUS CYST IN THE LIVER OF MAN. AFTER HUBER FROM
STILES

With the next parasites to be discussed, man functions as an intermediate host. The most distressing condition produced by these forms is echinococcosis, or hydatid disease, caused by infestation with *Echinococcus granulosus* or *Echinococcus multilocularis*. This is caused by infection with the ova of the dog tapeworm of the same name, a parasite which is almost universal in its distribution in this host. The intermediate host stages may occur in most of the domestic animals and the infection in dogs is kept up by their consumption of the larval stages of the parasite in meat or viscera

from such infected individuals. The infection in man is of the "blind alley" type, which unhappily does not lessen its severity.

When the "egg" of *Echinococcus granulosus*, from dog feces, is ingested it hatches in the intestine and sets free an embryo that penetrates the intestinal wall and reaches the circulation, where usually it is stopped by the liver; it may reach other tissues of the body, including the brain, long bones, heart, lungs, spleen or peritoneum. The development of the embryos is slow but in the course of perhaps a month after having reached their place of lodgment they appear as small globular bodies surrounded by a thick capsule made up of tissues elaborated from the host. Within this "cyst" which is ordinarily filled with a clear, sterile fluid, a peculiar type of asexual reproduction takes place, resulting in the production of a large number of additional scolices, and also smaller daughter cysts. Should the original cyst be ruptured accidentally these daughter cysts and scolices may develop new cysts in different parts of the body. Each of these scolices has the potential power of developing into an adult worm.

Diagnosis of the infection is extremely difficult in the early stages of the infestation as the symptoms of echinococcosis resemble those seen in numerous other diseases. The presence of a tumorous body, eosinophilia, and urticaria, should be considered suggestive. Exploratory puncture, which was formerly often resorted to is contraindicated, due to the hazards of bacterial infection and the possibility of bringing about discharge of the scolices into the peritoneal cavity. The use of x-rays which reveal the position of the hydatid cyst, offer the most precise information for diagnosis and treatment. Cure, when possible, is effected by surgical removal.

The important part of the present problem, from the particular point of view in which we are interested, is that this infection results from the consumption of eggs of the parasite from dog feces, made possible by close association with infected dogs or with other persons, such as shepherds, having close contacts with these animals.

Certain parasites, related to *Echinococcus granulosus*, such as the Multiceps (Coenurus) species, have also been reported from man. However, the six species known are all habitual parasites of certain animals. Gid, or coenurus disease of sheep, represents a type of this kind of infection. While the reports of human cases are not numerous, they indicate that man may harbor the larval forms of perhaps several of these related tapeworms of domestic animals.

Human infection with *Taenia saginata* and *Taenia solium*, the so-called beef and pork tapeworms, consists of intestinal infestation with the adult parasites in the great majority of cases. Consideration of these forms in detail will be found in a preceding chapter but as the mode of infection, with their larval stages may often be of the type under discussion here, a few words about them may not be out of place. In both of these species infection of man with the larval stage is in the nature of a "blind alley" infestation. In the case of *Taenia solium*, human infestations with its larval form, *Cysticercus cellulosae* are not infrequent and at least one case is recorded of infection with *Cysticercus bovis*, the larval stage of *Taenia saginata*. Such infections as these are produced by the ingestion of ova from feces of a human host who carries the adult worm. Obviously, self-infection is a possibility in such individuals. The tapeworm embryos released from the "egg" thus ingested reach the circulation by penetrating the intestinal wall, and are distributed throughout the body. After reaching their ultimate destination in the eye, heart, spinal cord, or muscle, they develop into cysticerci and may give rise to serious consequences such as epileptiform fits, convulsions, or other nervous derangement. The diagnosis of such cysticercus infections is discussed in the previous chapter to which reference should be made for details. Cure of these infections is impossible unless only a few cysticerci are present and in locations where they may be reached surgically.

Discussion of the intestinal protozoa of man also comes under the heading with which this section begins, but only a brief

consideration of these organisms is necessary, as their relation to human infection, via contaminated food, is largely a matter of chance, and cannot be considered in any sense obligatory. In contrast to the helminthic parasites previously considered under this heading, not all of the intestinal protozoa are immediately infective when passed but become so after a short period.

Of the amoebae found at times in the human intestine, *Endamoeba histolytica* appears to be the only pathogenic species. It has been found in about 9 per cent of all persons examined in the temperate zone. The majority of these infected individuals are true "carriers" and seldom exhibit clinical symptoms of amoebiasis, although they are discharging the infective stage of the amoeba, the cysts, in their stools the greater part of the time. In fact, it is only by means of these cysts that this organism can be disseminated, as persons suffering from diarrhea or dysentery discharge the amoebae in the motile non-infective stage. Spread of the infection to other persons thus necessitates ingestion of cysts in water or food contaminated with fecal material containing these forms.

The other intestinal amoebae found in man, *Endamoeba coli*, *Endolimax nana*, *Iodamoeba williamsi* and *Dientamoeba fragilis*, are harmless parasites and merit no further attention.

Among the intestinal flagellates of man the best known forms are *Giardia lamblia*, *Trichomonas hominis*, and *Chilomastix mesnili*, but here again no close connection exists between human infection with these organisms and food consumption.

Of the Sporozoa, all species of which are parasitic, very few except the malarial parasites are normally parasitic in man. None of the Sporozoa, except the malarial organisms are of prime importance in the production of human disease. Of greatest significance are the Coccidia, which frequently cause fatal diseases among the lower animals. Of recent years cases of human coccidiosis have been frequently reported and it seems probable that human coccidia are more numerous than

has previously been thought. In some cases coccidia in man cause little inconvenience, while in animals, these infections frequently terminate fatally. The means by which human infection is acquired is through the ingestion of food or water containing the oöcysts of the organism which have been discharged in the feces from an infected person. Other means by which the coccidia are disseminated are the unsanitary habits of certain individuals, and by means of flies, which have had access to feces containing the organisms.

The only species of Coccidia thus far described as a human parasite is *Isospora hominis*.

Diagnosis of coccidiosis rests on recognition of the oöcysts in a smear preparation of feces made by rubbing up a bit of fecal material in a drop of physiological salt solution. Such a preparation covered with a cover-glass and examined under reasonably high magnification, enables one to recognize the oöcysts.

Among the Infusoria or ciliates there are many free living species but there are also a large number of species parasitic in vertebrates and invertebrates. Of these, *Balantidium coli*, normally parasitic in swine, is the only one found with any frequency in man. Other species have been reported from man, however.

Balantidium coli, is second in importance only to *Endamoeba histolytica* as a cause of human dysentery. Although normally an inhabitant of the large intestine this organism, like *Endamoeba histolytica*, has the power of invading the tissues causing ulceration. Among cases of balantidial dysentery the mortality rate is high.

The dissemination of *Balantidium coli* infection is through distribution of the cysts of the organism in the feces. These cysts taken into the alimentary canal in contaminated food or water then give rise to infection in the new host.

Diagnosis of *Balantidium coli* infection is based on identification of the ciliates in fecal suspensions examined under low power magnification. There is nothing in such suspensions

that is liable to be confused with these forms because of their large size and peculiar characteristics.

II. HELMINTHIC PARASITES OF MAN, ONLY BECOMING INFECTIVE AFTER UNDERGOING A CERTAIN AMOUNT OF DEVELOPMENT IN THE ENVIRONMENT, INFECTION WITH WHICH IS ACQUIRED THROUGH INDIRECT FECAL CONTAMINATION OF FOOD OR OF THE LIPS (TABLE IV).

In the group of infections considered under this heading we begin to have food acting as the usual vehicle by which the infective agent is transmitted. Whereas in the preceding group of infections the ova of the parasites were seen to be directly infective when passed in the stools of the host, here we have to do with a group of parasites the ova of which must undergo a relatively long period of development in the open before becoming infective. This period varies from a few days to several weeks, depending on environmental conditions. During such time the original stool portion is usually quite destroyed or broken up, and the infective organisms reach human hands or food again, by which they are transferred back to the mouth. Included here are probably the two most common nematodes of man, both intestinal forms, namely, *Trichuris trichiura* (*Trichocephalus dispar*), the whipworm, and *Ascaris lumbricoides*, the large round worm, as well as the dog and cat ascarids, *Toxocara canis* (*Belascaris marginata*), and *Toxascaris leonina* (*limbata*), which also occasionally infest man. Certain related nematodes whose life histories are incompletely known also evidently belong here, but no trematodes or cestodes are included in this type of infection.

Trichuris trichiura is a cosmopolitan parasite, which has been generally considered a human form, although the pig whipworm may represent the same species according to Schwartz (4). Being easily observed in fecal material the widespread campaigns against hookworm have revealed an incidence of *Trichuris trichiura* which frequently reaches 50 per cent or more of the population. Ordinarily the human host

TABLE IV
Helminthic parasites of man, only becoming infective after having undergone a certain amount of development in the environment, infection with which is acquired through indirect fecal contamination of food or of the lips

GROUP	NAME OF PARASITE	OTHER NAMES, SAME ORGANISM	RESERVOIR HOSTS	PART OF HUMAN BODY PARASITIZED	GEOGRAPHICAL DISTRIBUTION	RELATED FORMS WITH PROBABLY SIMILAR METHODS OF INFECTION
Trematodes	None					
Cestodes	None					
	<i>Trichuris</i> tri- <i>chiura</i>	Whipworm	Man (pig?)	Intestine; cecum, appendix, colon and erratic loca- tions	Cosmopolitan	
	<i>Ascaris lumbr- icoides</i>	Common roundworm	Man (pig?)	Intestine	Cosmopolitan	
	<i>Toxocara canis</i>	Dog ascaris	Dog	Intestine	Cosmopolitan	
	<i>Toxocara leo- nina</i>	Cat ascaris	Cat	Intestine	Cosmopolitan	
Nematodes						Other ascarids reported from man include <i>Fusaria maritima</i> in Greenland, <i>F. texana</i> in Texas, as intestinal parasites, and <i>Lago- cheruscaris minor</i> from Trinidad in subcutaneous abscess

has only a few of these worms at a time. The adult trichurids in the intestine, most frequently in the cecum, are partially embedded in the wall. They are not infrequently found in the appendix, and in the colon.

The female trichurids lay relatively large numbers of eggs which appear in the feces, usually in the one-cell stage. Following their expulsion they require a period of development in the open, that is, until the embryo is fully developed within the shell, before they are re-infective upon swallowing. This developmental stage may require several days or several weeks, depending upon the environmental conditions, chiefly on the temperature and oxygen supply. Their pathological action as adults in the intestine, is more or less disputed. Some authorities have held them a causative factor in appendicitis. The worms are difficult to dislodge with anthelmintics, apparently because they are so far down in the intestinal tract and so well buried in its walls as to be difficult of access by drugs.

The most common and widespread human nematode, is the cosmopolitan *Ascaris lumbricoides*. This species is indistinguishable morphologically from *Ascaris suilla*, found in swine, but recent studies by Koino (5); Payne, Ackert and Hartman (6), and Caldwell and Caldwell (7) indicate that the pig form does not, at least freely, infect man, contrary to the usual opinion. From the public health standpoint their distinction as physiological strains, should still be accepted with caution.

The adult ascarids, which attain the length 15 to 40 centimeters and have a diameter of nearly one and a half centimeters are often present in large numbers and occur in the lumen of the small intestine, into which the gravid females pass enormous numbers of eggs (see Cram (8)). These eggs, after being swept out with the feces, likewise require a period of development in the open. Depending on environmental conditions the ova require from a week to several weeks to produce infective embryos. During this period they are very resistant to inimical agents, such as drying and chemical disinfection. *Ascaris* eggs, indeed, are remarkable for their ability

to withstand adverse conditions. They are cultivated in the laboratory, for instance, in a solution of formalin.

It was formerly believed that the development of *Ascaris*, once the embryonated eggs had been ingested, was simple and direct; that the embryos having been released from the eggs in the intestinal tract, went on immediately to become adults there. It is now known, especially through the work of Stewart (9), Ransom and Foster (10), and Ransom and Cram (11), that a large number of the organisms upon hatching, penetrate the intestinal wall and reach the circulation, eventually being stopped in the lung capillaries because of their large size. Here, through their motility, they break into the alveoli, and make their way eventually into the trachea and back of the mouth, where they are swallowed. Subsequently, on their second arrival in the intestine they apparently remain and grow to adult size.

When large numbers of the larvae go through the lung migration at about the same time distinct pathological signs of their passage become evident, even to the production of pneumonia. In pigs this lung migration is the chief cause of the disease known as "thumps" and some of the obscure respiratory manifestations in children may be due to the same cause.

In the intestine the adult worms may occasionally occur in such numbers as to cause bowel obstruction, and even when few in number, a variety of intestinal and nervous symptoms in children have been referred to them. A recent review of this problem by Cram (12) will be found especially valuable.

The worms free in the intestine are not particularly resistant to proper anthelmintics of which oil of chenopodium and santonin appear to be the most effective. They are slowly eliminated from the intestine even after partial dislodgment.

Occasionally the ascarids reach other parts of the body, due either to their entrance into the circulation as larvae, or to their wandering habits as adults, especially under conditions when the host is febrile or moribund. Their most frequent secondary location is in the gall ducts, although there are many

records of their passage up the esophagus. They may be sometimes passed spontaneously in the stool.

The cat and dog ascarids, *Toxascaris leonina* and *Toxocara canis* have life histories similar to that of *Ascaris lumbricoides*, but the eggs are more promptly infective after passage in the feces than is the case with the latter species. Related forms known from man with probably similar life histories are *Fusaria maritima* reported from Greenland, *Fusaria texana* (*Ascaris lumbricoides*?) from Texas, and *Lagocheilascaris minor* (of *Felis* sp.?) reported from Trinidad in a subcutaneous abscess.

Several other nematodes, reported occasionally from man, appear probably to be transmissible by the general method here under discussion, namely, a stage—egg or larval—which becomes infective sometime after passage in the feces. They are not given in Table IV but include three species of *Oesophagostomum* and five species of *Trichostrongylus*.

III. HELMINTHIC PARASITES OF MAN, INFECTION WITH WHICH IS ACQUIRED THROUGH THE INGESTION OF AN ARTHROPOD INTERMEDIATE HOST, CONTAINING THE LARVAL STAGE (TABLE V)

With the exception of *Dracunculus medinensis*, the guinea worm of man, the organisms here described are of secondary importance as human parasites, but their mode of transmission illustrates another stage in the development of an absolute dependence upon food or water as the means by which the infection is carried. Less often, it may be presumed, are arthropod intermediate hosts ingested directly from unclean fingers than from more or less grossly contaminated food or drink. In the case of *Dracunculus*, the typical mode of infection is from water containing infected cyclops—the intermediate host—rather than from food. No trematodes are included here, the nematodes are few, but the peculiarities of cestode life histories particularly, find illustration in this group.

Dipylidium caninum, the dog tapeworm, and *Hymenolepis*

TABLE V
Helminthic parasites of man, infection with which is acquired through the ingestion of an arthropod intermediate host which contains the larval stage

GROUP	NAME OF PARASITE	RESERVOIR HOSTS	INTERMEDIATE HOSTS REQUIRED TO BE INFESTED	PART OF HUMAN BODY PARASITIZED	GEOGRAPHICAL DISTRIBUTION	REMARKS
Trematodes	None			General in tissues	Africa; Orient; U. S. A.	
	<i>Sparganum</i> sp.	Not known (cats, dogs?)	Not known (cyclops?)	Intestine	Russia; Orient; Guyana	Three species reported from man
	<i>Davainea</i> sp.	Not known	Not known (cockroaches?)	Intestine		Three species reported from man
Cestodes	<i>Diphyldium caninum</i>	Dogs, cats	Fleas and lice of dogs and cats	Intestine	Cosmopolitan	
	<i>Hymenolepis diminuta</i>	Rats	Beetles, meal worms, fleas, myriapods	Small intestine		Probably cosmopolitan
Nematodes	<i>Dracunculus medinensis</i>	Man, perhaps various carnivora	Cyclops sp.	Subcutaneous, especially limbs and back	India; Africa	

diminuta, the rat tapeworm, are both of practically cosmopolitan distribution in their normal hosts. Both parasites, moreover, are being found more frequently in man as widespread fecal examinations become the rule in various parts of the world. *Dipylidium caninum* has as its intermediate hosts the fleas of dogs and cats, while *Hymenolepis diminuta* is known to develop its larval stage in beetles, meal-worms, fleas and myriapods. The ingestion of one of these arthropod intermediate hosts permits the larval cestode to emerge in the intestinal tract, where it goes on to sexual maturity. Diagnosis is based primarily on the identification of the egg of the tapeworm in the feces.

Three species of *Davainea* which have been reported from man in Russian Turkestan, Formosa, Tokyo, the Philippines, Siam, Mauritius and Guiana, are similarly transmitted in all probability. The adult parasites live in the human intestine, the reservoir hosts are mammals and birds, and the cysticercoid larvae occur in arthropods and perhaps molluscs, with the cockroach a suspect. Diagnosis of infestation is made by finding the eggs in the feces.

Another group of cestodes of importance, having this type of transmission, is the *Sparganum* species, larval pleroceroid tapeworms which become tissue parasites, especially subcutaneously. The life histories of these organisms are not well understood, but from the larval stages and some experimental observations, they are held to be rather close relatives of *Diphyllobothrium latum*, the broad tapeworm of man. They have their normal adult stages in cats or dogs; the infections in man are thus of the "blind alley" type, as in the case of *Cysticercus cellulosae*, the pork tapeworm. Three species of *Sparganum* have been reported from such widely separated areas as German East Africa, China, Japan and the United States. It is possible that the parasites are contracted by ingesting an infected second intermediate host, as a frog or fish, but more likely they are acquired from the first intermediate host, which is probably the fresh-water crustacean, *Cyclops*.

Of especial interest is infection with *Dracunculus medinensis*, the guinea worm, which is the cause of dracontiasis. This disease has been known from ancient times in the Near East, and is held to be the "fiery serpent" referred to by Moses. It is common as far east as in India, and occurs in the interior as well as coastal regions of Africa. While the parasite is present in other mammals, as the ox, horse, dog or leopard, it is to be considered primarily as a human parasite. The adult form of the worm lives in the subcutaneous tissues, especially



FIG. 25. NATIVE METHOD OF EXTRACTING *DRACUNCULUS MEDINENSIS* BY WINDING THE WORM UP ON A STICK. AFTER BLANCHARD

of the arms, back and legs, where it may often be felt or seen and diagnosed as a sinuous structure about one-sixteenth of an inch in diameter and often as much as three feet in length. When the female is gravid, which is about a year after infection, a vesicle develops in the skin near the anterior end of the worm. This ulcerates and in the bottom a small hole forms through which a portion of the uterus of the worm is prolapsed. At this time the female is filled with embryos and when water is splashed on this ulcer a milky fluid containing a great number of embryos escapes. This continues at intervals when the area is wet, for about a fortnight, until the embryos have largely escaped. The natives of Africa and India

especially, fasten the protruding portion of the worm to a stick with which it is gradually extracted. If under these circumstances, the worm is ruptured, the embryos escape into the tissues where a rather violent reaction occurs. Inflammation, fever, abscesses and sometimes death are frequent consequences of the discharge beneath the skin of the chylous fluid containing the embryos.

The number of adult worms present in an infected individual is small, often only one or two, although as many as fifty have been reported.

The embryos which escape under the stimulus of water splashed over the cutaneous ulcer swim about for two or three days, during which interval they penetrate or are ingested by a species of fresh-water crustacean, the cyclops. In this host they undergo a certain period of development, covering four or five weeks, following which they are able to re-infest man when the cyclops is ingested in drinking water. Thus the pools in desert places where cyclops is found, come to be foci of infection.

The areas of the world where infection with *Dracunculus medinensis* is endemic are those regions in which filtration or boiling of drinking water is not practiced, a type of prophylaxis which is as sure and simple, and under native conditions, probably as impossible of attainment as would be the control of hookworm infection through the universal wearing of shoes in the tropics. Disinfection of wells and pools by heating the water with steam or by the addition of small amounts of potash which will kill the cyclops has also been suggested as a means of preventing human infection with these worms.

IV. PARASITES OF MAN, INFECTION WITH WHICH IS ACQUIRED
THROUGH THE INGESTION OF SOME FOOD SUBSTANCE, IN
OR UPON WHICH THE LARVAE HAVE ENCYSTED
(TABLE VI)

The transmission of these parasites is obligatory by way of food, with a particular food substance acting as the vehicle

for the transmission of each parasite. These infections thus differ from those that have been earlier described, which depend upon more or less gross food contamination for their transmission, when it is by food rather than by direct contamination of the lips that they are transferred. While most of the worms, in which transmission by food is obligatory, are trematodes, certain cestodes and nematodes are also transferred in this fashion. Besides the species known to be transmitted in this way, there are other forms which will likely be included when the details of their life histories are understood. Prophylaxis against all these parasites must be directed against the ingestion of certain limited foods, which vary with the species of parasite concerned.

Hepatic Distomiasis

Among the trematodes we may include the species of fluke whose life history was among the first to be well understood, *Fasciola hepatica*, the sheep liver fluke, which has been reported from man on numerous occasions in Europe, Africa and America. This is a common parasite of sheep throughout the world, but it occurs in other mammals, especially herbivora, which serve as a reservoir of human infection. The adult flukes are found in the gall ducts, from whence ova escape with the bile and later through the feces, to the environment. After the developmental stages are passed in the snail, as is typical of all trematodes, the larval forms or cercariae, escape into water and encyst upon plants or leaves in the water or at the edge of the streams or ponds. When the infested plants are ingested, the cercariae escape in the intestine and the young flukes migrate into the bile ducts where they mature.

One case of *Fasciola gigantica* infestation in man has been reported. The infection was probably contracted in Africa.

An atypical infestation with young *Fasciola hepatica* is known in Syria. Through the practice of eating raw livers, especially of goats, immature flukes are occasionally ingested, which escape mastication, lodge in the upper pharynx and

TABLE VI
Parasites of man, infection with which is acquired through the ingestion of some food substance, in or upon which the larvae have encysted

GROUP	NAME OF PARASITE	OTHER NAMES, SAME ORGANISM	RESERVOIR HOSTS	FOOD AND PARASITIC STAGE INGESTED	PART OF HUMAN BODY PARASITIZED	GEOGRAPHICAL DISTRIBUTION	REMARKS
	<i>Fasciola hepatica</i>		Sheep, goats, cattle	Grass and plants with encysted cercariae Goats' livers with young flukes	Gall ducts and erratic locations Mucosa of mouth and pharynx	Europe; Africa; Americas Syria	Causes fascioliasis Causes halzun
	<i>Fasciola hepatica</i>		Sheep liver fluke	Ruminants	Plants with encysted cercariae	Africa	One case only reported from man
	<i>Fasciola gigantica</i>		Large human intestinal fluke	Man, (pigs?)	Water catops and water chestnuts with encysted cercariae	Asia; especially Chekiang province China; Egypt	Causes fasciolopsiasis
	<i>Fasciolopsis buski</i>		Lung fluke	Man, many mammals	Crabs and crayfishes with encysted cercariae	Asia, especially Formosa and Korea	Causes paragonimiasis
Trematodes	<i>Paragonimus westermani</i>			Man, cats, dogs	Fish with encysted cercariae	Europe; Siberia; Tonkin; China; Japan	Other species reported from India and Siam
	<i>Opisthorchis felineus</i>		Human liver fluke	Man, dogs, cats, pigs	Fish with encysted cercariae	Egypt; Japan; China	Causes clonorchiosis
	<i>Cnemidocaris sinensis</i>		Small intestinal fluke	Man, dogs, cats	Fish with encysted cercariae	Formosa; Japan; Korea	Related to <i>Stamnmasoma</i> sp. and <i>Monorchotrema</i> sp. also reported from man in Japan and Formosa
	<i>Heterophyes heterophyes</i>						
	<i>Metagonimus yokogawai</i>		Small intestinal fluke	Man, dogs, cats	Fish with encysted cercariae		

Cestodes	<i>Diphyllobothrium latum</i>	Broad tape-worm	Man, dogs, cats	Fish with plerocercoids	Small intestine	Europe; Asia; Africa; U. S. A.	Related to <i>D. cordatum</i> from Greenland and <i>D. plagenporus</i> sp. from Romania and Japan, also reported from man
	<i>Taenia solium</i>	Pork tape-worm	Man	Pork with cysticerci	Intestine	Also reported from man	
	<i>Taenia saginata</i>	Beef tape-worm	Man	Beef with cysticerci	Intestine	<i>T. infenvis</i> (<i>T. crassicaulis</i>) from Argentina, and <i>T. confusa</i> from U. S. A.	Also reported from man
	<i>Trichinella spiralis</i>	"Trichina worm"	Rat	Pork with encysted larvae	Adults in small intestine; larvae in muscles	Causes trichinosis	
Nematodes						Cosmopolitan; especially Germany and U. S. A.	

attach themselves to the mucosa. Here they produce a disease known as halzoun, which lasts from several hours to several days, and is characterized by swelling and inflammation, which may be severe, and not infrequently leads to suffocation and death. After vomiting, natural or induced, recovery takes place.

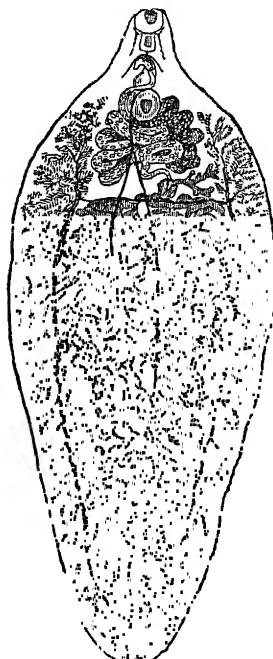


FIG. 26

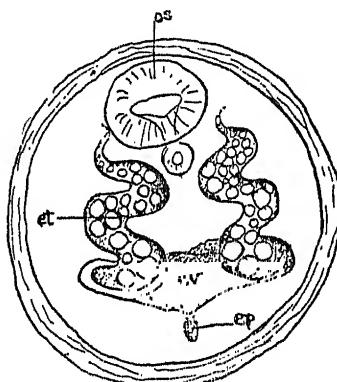
FIG. 26. *FASCIOLA HEPATICA*. $\times 3.2$. AFTER LEUOKART

FIG. 27

FIG. 27. CYST OF *FASCIOLOPSIS BUSKI*

Showing bladder terminals full of concretions and the excretory vesicle partly distended: (os), oral sucker; (et), excretory tubule; (ev), excretory vesicle; (ep), excretory pore. After Barlow.

Fasciolopsiasis

The disease caused by infestations with *Fasciolopsis buski*, the large intestinal fluke, is known as fasciolopsiasis. The organism was first discovered by Busk in 1843, in the duodenum

of a Lascar sailor dying in London. During the next 66 years only a few cases were reported and the parasite was believed rare, but in 1909 Ward (13) stated that the "species is far more abundant and of much greater importance than has hitherto been believed." Since that time, knowledge of this parasite has been greatly increased, especially by the work of Goddard (14), Nakagawa (15), and Barlow (16, 17). It is now known to cause a common and very serious infestation of man in Northern Chekiang, China, centering at Shaohsing, not far from Shanghai. Besides this large central reservoir, the parasite is widely disseminated, "being reported from many parts of China, as far north as the Yangtze Valley and as far west as Chengtu and Suifu in Szechwan province, and throughout the southern provinces. It has also been reported from India, Assam, Siam and the neighboring Malay Archipelago. It would not be strange to find it in the Philippines and in the Hawaiian Islands, because of the migration of Chinese to those parts in large numbers. The Shaohsing area, which is the most heavily infected endemic center, covers an area of about 1,600 square miles. In this area the disease profoundly affects the life of between a million and a million and a half of people, reducing their efficiency and causing a great loss of life. Nearly all of the cases come from a district lying north of the southermost limits of the city of Shaohsing and extending out in a fan-shaped area to the east and west. This may be explained by the drainage conditions obtaining here. Three rivers rise in the hills to the south, and flow through the city out into the canal system of the plains of silt to the North. The parasite develops best in quiet water, and the intermediate hosts do not live in rapidly flowing streams which probably explains this phenomenon" (Barlow (17)).

In Cochin-China, and especially in Formosa, the infection is common in pigs, with a reported absence of any large amount of infection in man in the same areas. The parasites from man and the pig are indistinguishable morphologically.

The excellent work of Nakagawa and Barlow, within the last

few years, has cleared up the life history of this form, which in many respects resembles that of the somewhat closely related *Fasciola hepatica*. Despite the description of several species of *Fasciolopsis*, it seems very probable that only one species *Fasciolopsis buski*, is involved in the production of human disease.

The following account is from Barlow's (17) recent monograph on the life cycle of *Fasciolopsis buski*.

The sexually mature forms, which live in the small intestine, usually measure from 13 to 48 mm. in length, although this figure varies, depending on conditions under which the flukes are held before measurement, their soft bodies being very susceptible to change in size. In the intestine they lay great numbers of eggs which escape in the feces, Stoll, Cort and Kwei (18) recently reporting the finding of about 25,000 per fluke per day. These ova are in the one- or two-celled stage, and require from 16 to 77 days, with an average of 45 days, to develop a miracidium or free-swimming larva, which then escapes and enters a snail, either *Planorbis schmackeri* or *Segmentina nitidellus*.

After a developmental cycle in the snail, cercariae escape and shortly encyst, the process of encystment occupying from one to three hours. Preferred places of encystment are "water-grown plants which the people eat raw, especially the water caltrop and the *Eliocharis tuberosa*," or "Water chestnut." Over 200 cysts have been found on the skin of one water caltrop although the average number is usually about twenty to thirty. The transfer to man occurs usually from eating these water nuts raw, for the cysts are set free into the mouth while the "nuts" are being peeled with the teeth. "Being spherical and of great lubricity, as well as being very small, it avoids being crushed and reaches the stomach intact. Here it is protected from digestion by its keratin-like coat, which is not affected by gastric juices. When it reaches the duodenum, however, contact with the intestinal juices dissolves away the cyst wall, and frees the inclosed metacercaria which attaches



FIG. 28



FIG. 29

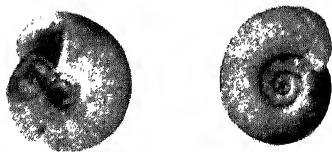


FIG. 30

FIG. 28. CALTROP PLANT AND NUT WITH *PLANORBIS SCHMACKERI* SNAIL TO THE LEFT OF THE NUT. AFTER BARLOW

FIG. 29. THE APPEARANCE OF A CHILD WITH FASCILOPSIASIS IN NOT VERY SEVERE FORM; EDEMA AND ASCITES PRESENT. AFTER BARLOW

FIG. 30. VENTRAL SURFACE OF *PLANORBIS SCHMACKERI* SNAIL SHELL TO THE LEFT; DORSAL SURFACE TO THE RIGHT. $\times 2$. AFTER BARLOW

FIG. 32. THE HUMAN LIVER FLUKE, *CLONORCHIS SINENSIS*

(*c.l.*), Laurers canal; (*dst*), vitellaria; (*ex*), excretory bladder; (*h*), testes; (*k*), ovary; (*r.s*), receptaculum seminis; (*vd*), vas deferens. $\times 4.5$. After Looss.

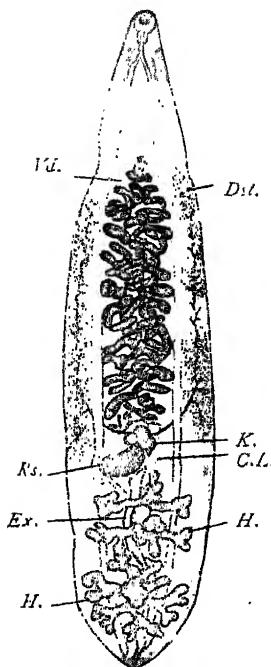
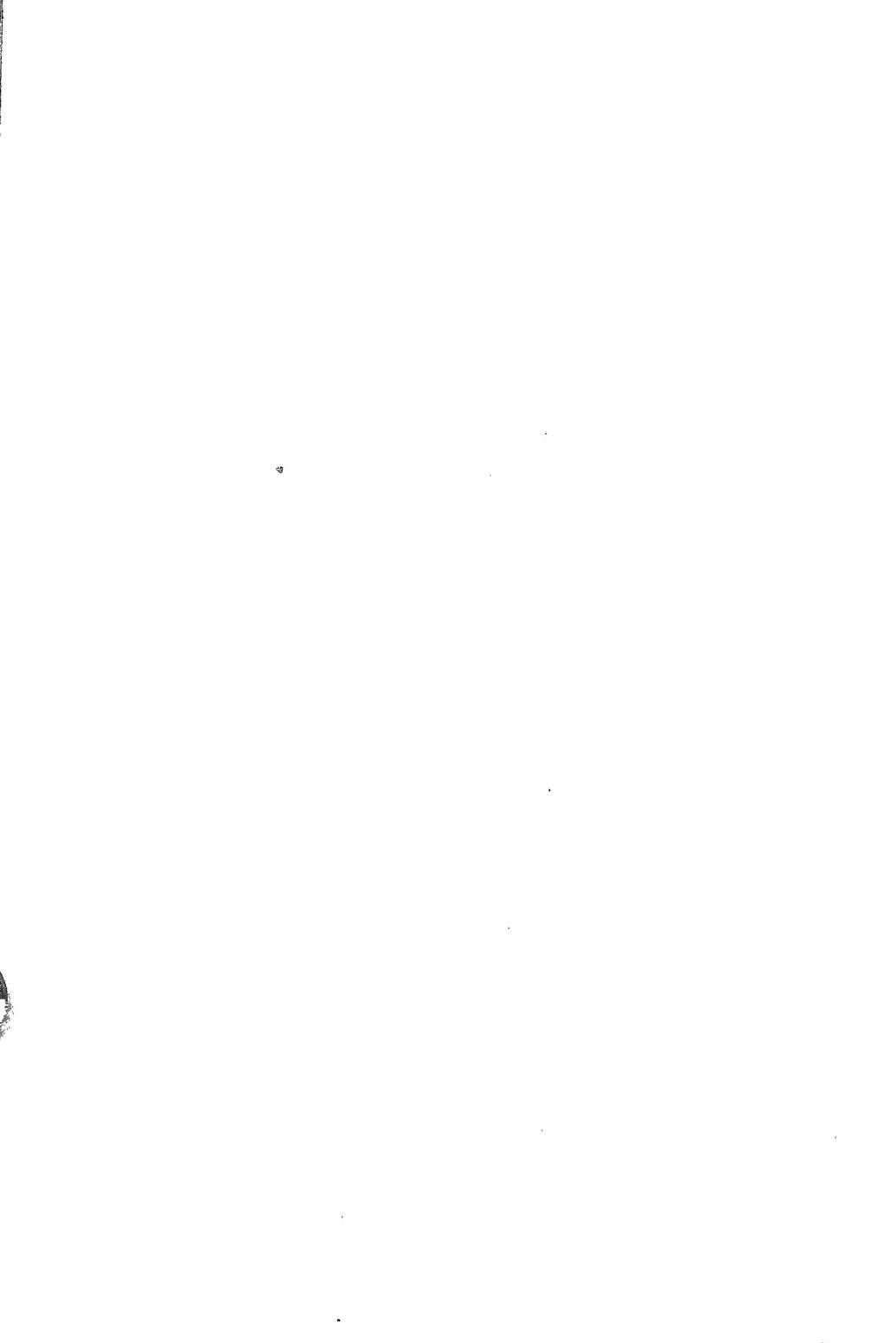


FIG. 32



itself to the wall and begins its rapid growth to maturity." There is no wandering in the body with this form as with *Paragonimus*.

"Symptoms come on in gradually increasing severity as the infestation gets older. The flukes live in the upper part of the small intestine and eat the food contents of the same. Their growth may be hindered by the action of their own excretions. Undoubtedly it is these secretions which cause the symptoms in the definitive host. Oedema comes on within 20 days of infestation. There is little or no anemia and when it appears it is not primary anemia. The oedema does not involve the chest. Diarrhoea alternates with constipation in most cases. The stool is not noticeably offensive."

There is but one pathognomonic sign of fasciolopsiasis, and that is the finding of the egg in the stool. This egg is large and not easily missed in fecal examinations. It may be confused, chiefly, with the ovum of *Fasciola hepatica*, to which "there is a marked similarity in size, shape, and general appearance. This would be truer in ova appearing from both flukes in the same stool, for they would then be of the same color. . . . The contents of fasciola ova, as they appear in the feces of the water buffalo and yellow cow (in the Shaohsing region), are clearer, the yolk balls are fewer and contain fewer granules. In freshly passed stools, the ova show a marked difference in the germinal area. In fasciolopsis it is made out with difficulty and is seen in very few ova upon cursory examination. In fasciola it is seen in nearly all ova, and it requires no special care in focussing to bring it out. It lies nearer the center of the egg and is much larger than in fasciolopsis. . . . "

Treatment with either beta-naphthol or carbon tetrachloride is effective, and symptoms usually clear up rapidly once the worms are removed. Prophylaxis depends on the avoidance of the consumption of raw water chestnuts and water caltrops.

Paragonimiasis

Lung fluke disease, or paragonimiasis, is caused by infestation with *Paragonimus westermani*. This trematode was first discovered by Westerman in 1877 in the lung of a tiger from the zoological gardens in Amsterdam. Two years later Ringer found a similar fluke in a Portugese living in Formosa. In 1880 Baelz described a parasitic haemoptasis, believing it a gregarine disease, and in 1883 four Japanese collaborators in Yokohama found the fluke at autopsies. By 1890 it was known to be fairly prevalent in Japan. While endemic cases of this infestation in man have not been reported from the United States, flukes believed to be of the same species have been found in the cat in Michigan, and in pigs in Cincinnati. At present, except among the natives of Formosa, and in somewhat isolated villages, especially along swift mountain streams in several provinces of Japan and Korea, it is not prevalent anywhere in the world. Cases have been reported, however, from Peru, Yucatan, Mexico and Tripoli, although definite endemic centers have not, apparently, been established.

While the organism has thus been known for a long time, the details of its life history have been described only in the last dozen years. Nakagawa (19), in Formosa, found the larval stage encysted in the fresh-water crab, *Potamon obtusipes*. Yokogawa later infected mammals from crabs. Ando (20), in 1920, furnished the completed life history. The normal site of the adult fluke is in the lung, in loose connective tissue "cysts," which usually come to communicate with the bronchi or bronchioles. The eggs are thus coughed up and are either expectorated, or swallowed, and escape with the feces. The egg requires a period of 3 to 4 weeks to develop and hatch outside the body. When the eggs hatch a miracidium escapes and penetrates snails of the *Melania* species. From the snails cercariae later escape and encyst in several crustacea, the second intermediate host not being highly specific with this parasite. Besides *Potamon obtusipes* in Northern Formosa and Southern Japan, it is found in *Potamon dehaani* and

Potamon sinensis, in *Eriocheir japonicus*, a large "hairy" crab common in small streams in Japan, in the crayfish, *Astacus similis*, in Korea, and probably in others.

In the endemic districts a large percentage of the crabs have cysts one report from Formosa showing that four-fifths of the crabs are infected. In another investigation, where it was shown that half the aborigines had the parasites, cysts were found in all the suspected crabs examined.

The cysts are often numerous in a single crustacean, over a thousand having been counted in a single crayfish. These are



FIG. 31. THE LUNG FLUKE, *PARAGONIMUS WESTERMANI*, SEEN FROM THE VENTRAL SURFACE

distributed generally throughout the animal, although, usually, most of them are found in the gills and muscles, especially of the cephalothorax. The encysted cercariae have a cyst wall, apparently developed by the parasite, and are additionally protected by an outer host membrane.

From the crustacean intermediate host, theoretically, there are several ways by which man might become infected, as for example, through using the uncooked crustacea as food; by swallowing the cysts in drinking water after they have been

set free from dead disintegrating crustacea; or by eating uncooked or imperfectly cooked mammals in which the fluke has partially developed. Practically, the first method may be considered the only important one.

After the cysts are ingested, the young flukes are freed in the intestine. They shortly migrate through the intestinal wall into the body cavity where they evidently wander for some time during which interval they attain sexual maturity. Sometime during this period they penetrate the diaphragm, and upon reaching sexual maturity invade the lung from its outer surface. There is no evidence that they pass, either in blood or lymph, to this position. Not infrequently during this wandering stage flukes reach abnormal sites, even the brain.

Infections with *Paragonimus* often simulate tuberculosis. There is a chronic cough, usually in the morning. Expectoration, which can be produced at almost any time, gives rise to a rusty-brown sputum, its color coming partly from red cells, partly from the color of the numerous eggs. Hemorrhage may be occasional or frequent, and without apparent cause, although it is not so pronounced as in tuberculosis. Occasionally there are obscure abdominal symptoms. When there is cerebral involvement, the symptoms may simulate epilepsy.

The laboratory diagnosis rests on demonstration of the ova, either in the sputum or feces. These are relatively large, vary considerably in size—even from the same patient,—are yellowish-brown in color (darker brown in feces), and have a thick shell and an operculum. The ovum is in the one-cell stage when fresh.

Prognosis, in cases of pulmonary paragonimiasis, is usually good, but in the cerebral form of the disease it is unfavorable. Treatment is general and symptomatic, no specific for the eradication of the worms themselves being known.

Individual prophylaxis consists in avoiding improperly cooked crustacea as food. The cysts seem to be killed more easily than those of *Clonorchis* or *Metagonimus*. Cooking at

55°C. for 5 minutes kills them. Free cysts survived 0.2 per cent hydrochloric acid 3 hours, and vinegar 30 minutes. In Oriental Soy sauce they remain alive 1 hour but are killed in 9 hours.

Prophylaxis for a community may involve disinfection of sputum and feces, eradication of the snail or crab hosts, and prohibition of the use of uncooked crabs for food. The latter is difficult to enforce. The most feasible control seems to lie in destruction of the snails, which are large. Koboyashi reports that after killing *Melania* in a region, the percentage of crabs infected was demonstrably smaller than previously.

Clonorchiosis

Human liver fluke disease—the expression “human liver fluke” is used to distinguish this organism from the common sheep liver fluke *Fasciola hepatica*—or clonorchiosis is caused by *Clonorchis sinensis*. Infection with this parasite results from the peculiar food habit of certain Japanese and Chinese, whereby raw or partially cooked fish are ingested. This food habit, which is often seasonal in character, is responsible for keeping up the widespread infestations in the Orient.

Infestations with this worm were first described in 1876, by MacConnell from a Chinese in India, and by MacGregor, in Mauritius. Later, the area of its distribution was shown to be chiefly in Japan, Korea and China, principally South China, and extending to Siam, with scattering cases outside this zone in Chinese or Japanese who had acquired the infection at home. Recently, clonorchiosis has become of special interest in the United States as a cause for exclusion of immigrants. In both China and Japan the infection is quite widespread in dogs and cats.

The life history of *Clonorchis sinensis* makes clear the method of human infection, and also points to the necessary prophylactic measures. This worm has not only the typical life cycle of a trematode, including a stage of development in the snail, but the cercariae which come from the snail enter certain fish,

and encyst there. After ingestion in the fish, they then reach the mouth, intestine, and finally gall ducts of man, dog or cat, and do not infest the final host in any other way except through the mouth, and thus through food.

In more detail, the eggs of the adult worm escape with the bile to the intestinal contents and leave the host in the feces. Within the egg a ciliated embryo, the miracidium, develops, and hatching in fresh water, swims about and infects a snail *Bithynia striatula*. Following a course of metamorphosis and multiplication in the tissues of the snail, the small, tailed cercariae escape into the water and are able to penetrate under the scales and into the superficial muscles of several species of fish. They have been discovered in nature in at least 12 species of fresh water fish. Here they encyst, and can go no further in their development, until they are ingested by the final host.

Once in the intestines of man, they make their way into the bile ducts and gall bladder, where their damage seems referable primarily to the irritation and obstruction of the bile passages. The symptoms include tenderness and enlargement of the liver, more or less bloody diarrhea, jaundice, and often anemia, emaciation and weakness. In the severe infestations the patient frequently succumbs to intercurrent infection.

Laboratory diagnosis of clonorchiosis is through the discovery of *Clonorchis* ova in the feces. The eggs are quite small in comparison to other helminth eggs and are somewhat vase-shaped.

The lesions in the liver are related primarily to the irritant and obstructive action of the worms in the bile ducts. The clinical effect on the host, seems out of proportion to the mechanical effect alone, and a toxic factor may be present. At autopsy, the liver is hypertrophied, with surface blebs caused by the enlargement of bile ducts; on section old bile ducts are sclerotic and show as pockets, perhaps filled with fluid that itself is filled with eggs.

Microscopical lesions are of two types, in the bile ducts

themselves and in the parenchyma. The mucosa of the ducts shows great hyperplasia, sometimes so great as to be adenomatous, within which is new bile duct tissue. Or the mucosa may be destroyed locally. The surrounding tissues undergo intense hypertrophy, with sclerosis and much filtration with lymphocytes and eosinophiles. The parenchyma is often atrophied.

Treatment is chiefly symptomatic, with prevention of additional infection. Disinfection has proven difficult. In the absence of reinestation, many of the acute symptoms subside.

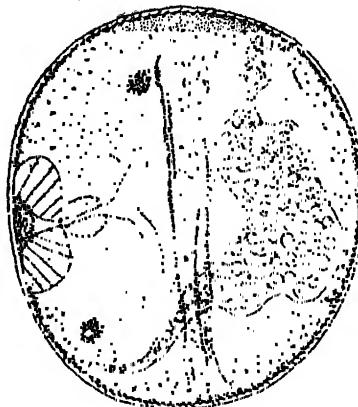


FIG. 33. CYST OF CLONORCHIS SINENSIS. AFTER FAUST

Most cases appear to be carriers, often the first knowledge of infection being the demonstration of the ova in the feces.

Prophylaxis against clonorchiosis consists primarily in a thorough cooking of fish which may be infested. In some districts in Japan, the eating of raw fish has been prohibited by law. Efforts have been made to eliminate the snail intermediate hosts in certain localities.

Certain rather closely related forms have been occasionally reported as parasites of man, and probably have similar methods of infection, through the consumption of raw or insufficiently cooked fish. These include *Opisthorchis felineus*,

a parasite of the dog and cat, found especially in northern Europe, and also in India and Japan. It has been reported from man in Leningrad and Siberia, and is regarded an important parasite near Omsk. *Opisthorchis novemcincta*, common in the pariah dog of India, was found at postmortem in two Mohammedans in Calcutta. *Opisthorchis viverrina*, a parasite of the civet cat in Siam, has been found in prisoners at Chieng-mai. There is little raw fish eaten in India, but the practice is not uncommon in Siam and is said to be on the increase, due to the food habits of immigrating Chinese coolies.

Another group of trematodes, which infest the intestinal tract of man through the ingestion of raw fish containing the cercariae, comprises several very small flukes belonging to the family Heterophyidae. Altogether, six species are now known, which have been found as natural human infections, or have been experimentally demonstrated as infective for man, namely, *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Monorchotrema tajihokui*, *Monorchotrema taichui*, *Stamnosoma armatum* and *Stamnosoma formosanum*. Of these *Metagonimus yokogawai* is evidently of most importance, not only because it may be of clinical significance, but also because it may be the most common trematode in man. This fluke has an egg which was confused with that of *Clonorchis sinensis* for many years, so that the earlier records of the incidence of both this worm and of human liver fluke infestation, based on fecal examinations, are considered untrustworthy.

Metagonimus yokogawai was discovered by Yokogawa in 1911 in cysts on the gills and under the scales of a small freshwater fish *Plecoglossus altivallis*, used as food in Formosa. Adults bred from these encysted forms by feeding them to dogs, were similar to other adults later recovered from man. The worm was described by Katsurada, who named it after its discoverer. *Metagonimus yokogawai* is common in dogs and cats in Japan and China, and following the differentiation of its ova was demonstrated as the commonest trematode in Japan. In Tokio an incidence of nearly 2 per cent was re-

ported, in Osaka 11 per cent, in Formosa 24 per cent. The life history of this form is evidently the typical one for a trematode parasite having three hosts and the second intermediate host, by which man is infected, is now known to be at least 18 different species of fresh-water fish.

The other members of the *Heterophyidae* are of less importance, but have the same type of life cycle, and finally reach man through the eating of infected fish. *Heterophyes heterophyes* was first reported as a human infection in 1851 by Bilharz in Egypt. *Heterophyes nocens*, described in 1915 by Onji and Nishio, in Japan, is regarded as the same as *Herterophyes heterophyes*. The two species *Stamnosomum armatum* and *Stamnosomum formosanum*, were first described from Japan. Faust and Nishigori (21) in 1926 reported the experimental infection of man with two other species of this group, *Monorchotrema taihokui* and *Monorchotrema taichui*. A fact of importance in connection with some of these forms, is that they are evidently normal parasites of both mammals and birds, and reservoirs for human infection may thus be quite widespread. The differentiation of these species by the eggs in the feces is possible, but difficult, and their possible confusion with the ova of *Clonorchis sinensis* is especially important. Faust and Nishigori (21) have given an excellent description of the differences, to which interested workers are referred.

Besides the above, there are a few quite unrelated flukes belonging to the *Echinostoma* whose detailed life history is not known but which are possibly transmitted to man by the eating of raw, or insufficiently cooked fish.

Finally, among the intestinal flukes, there are two species whose life history is not fully understood, but which may have a transmission to man that is obligate via some food. These are *Gastrodiscoides hominis*, and *Watsonius watsoni*.

Among the cestodes,—*Diphyllobothrium latum*, (*Dibothrioccephalus latus*) the broad fish tapeworm,—may be mentioned as an intestinal form of no inconsiderable importance in northern Europe, which has apparent endemic centers also in Asia,

Africa, and the northern part of the United States, and whose life history is dependent on a given food habit. Infection with this tapeworm is described in detail in the preceding chapter.

Other cestodes, depending on certain foods for transmission, are the cosmopolitan and familiar *Taenia saginata*, and more uncommon *Taenia solium*, infections with which are described in another chapter.

Among the nematodes, the organism of most importance, from the standpoint of food infection, is the so-called trichina worm, *Trichinella spiralis*. Infections from this organism are also discussed in detail in another chapter. Besides this species other nematode infections of man due to *Haemonchus contortus* and *Diectophyme renale* are of less general importance, but deserve mention.

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CHAPTER XVII¹

DIAGNOSIS OF HELMINTH INFESTATION

Methods of diagnosis. Technique of making fecal examinations. Spurious parasitism. Key for the identification of eggs of human helminths.

The helminths which infect man by way of the mouth, either optionally or necessarily in food, may be separated into two groups from the standpoint of diagnosis, namely, the tissue parasites, and intestinal parasites, that are free or attached in the intestine or its diverticula. Every species which infects man by way of the mouth and food, has it is true, an intestinal stage. For those which become tissue invaders, however, this is usually transient and unrecognized, as for instance in the case of *Paragonimus westermani*. A few forms have a kind of temporary pseudo-tissue parasitism, followed by residence in the intestinal tract proper, as in the case of *Ascaris lumbricoides* and *Hymenolepis nana*. These are properly considered, under diagnosis, as intestinal forms. With *Trichinella spiralis*, however, there is a certain period in which the adults are in the intestine, and may even be recovered in the stool following anthelmintics and purging, after the beginning of invasion of the musculature by the embryos, the symptoms from which call attention to the parasitism.

In general, the tissue parasites are diagnosed by clinical symptoms which may be distinctive enough to give a true diagnosis, as in infection with *Dracunculus medinensis*, or may remain temporarily or permanently obscure unless the tissues involved are susceptible of surgical excision, either for diagnosis alone or for cure. Many of the tissue parasites of interest to us in this discussion are frequently subcutaneous in position, and thus accessible. This is not uniformly true, since infesta-

¹By Norman R. Stoll.

tions with *Paragonimus westermani* are usually inoperable, while those with *Echinococcus granulosus* are sometimes so.

Diagnosis of those forms which reach sexual maturity in the intestine and gall ducts, rests fundamentally on recognition of the ova in the feces. The simplest and most used method is by means of the so-called "smear," which may be examined either naked or covered. It is made by puddling a small amount of fecal material in a drop of water, or physiological saline, on a slide. A toothpick is a convenient applicator, a clean one being used for each new fecal specimen. It is preferable to sample feces from several parts of the stool. The "emulsion" on the slide should be thin enough to permit easy observation, and yet be concentrated enough to allow the examination of a fair amount of feces. The usual rule followed, is that the fecal film shall not be so dense but that news print shall be readily observed through it. Despite certain limitations of this method, and the abundance of newer methods of fecal diagnosis for helminthic ova, the smear method still holds a deservedly important place in technic. This is particularly true when its limitations are understood and taken into account in the interpretation of results. Hau-sheer and Herrick (1) have recently pointed this out in connection with hookworm diagnosis, for instance, and their arguments are referable to infections with other intestinal nematodes, and also other helminths.

While the typical helminth lays great numbers of eggs, there are conditions when the individual infestations are very light and the smear method may reveal them only after considerable searching by the microscopist. Other methods have been devised, therefore, designed to either hasten or ensure diagnosis, or both. For the most part, these methods have turned on the two principles of concentrating the eggs by sedimentation or centrifugation, with decanting off of the supernatant floating fecal debris, or,—in the case of the nematode ova particularly—floating them to the surface of a mixture made with a fluid of high specific gravity. The variations in the details of method founded on these two basic principles are very nu-

merous. The concentrative method in its simplest, and one of its most usable forms, necessitates comminution of a nugget of feces in water and sedimentation or centrifugation either with or without first straining out the coarse debris. The mixture is then decanted, and the process of suspension and concentration repeated until a nearly clear supernatant fluid results when a portion of the sediment is removed by a pipette to a slide and examined after the simple smear method. Such a technic is usable for practically all ova of intestinal helminths. Its principal drawback is the time required for the manipulation. Its advantage lies in the fact that relatively large quantities of stool may be dealt with, if desired, and the eggs are usually distorted little, if at all, because they have not been subjected to any strong osmotic action.

In the floatation methods, which are useful primarily for nematode ova, the feces are stirred up with solutions of about 1:200 specific gravity. Such solutions are saturated sodium chloride, magnesium sulphate, glycerin, or 30 per cent sugar,—made by dissolving granulated sugar in an equal amount by weight of cold water. In this way ova are freed from the stool particles and after standing for 10 to 30 minutes, samples of the surface layer are transferred to a slide and examined. Transfer is accomplished by a loop of wire, the open end of a vial, or by laying the slide face down on the preparation, which has been filled to a proper point in its container. A recent combination of the two methods of concentration and floatation is that of Lane (2) which gives unusually good diagnostic preparations for examination with the microscope. Most textbooks and papers dealing with surveys of the incidence of intestinal parasites give details of these various methods. A few of the more important articles on the methods themselves are those by Hall (3), Hickey (4), Willis (5), Lane (6) and Hausheer, Herrick, and Pearse (7). The three latter deal primarily with methods for revealing nematode ova.

Within recent years efforts have been renewed to measure the amount of individual infestation with the parasites whose ova occur in the feces, by the indirect method of determining

the egg output. Due to the great fecundity of parasitic worms, this has proved a feasible procedure, and has the advantage of giving a measure of the intensity of parasitism without disturbing or dislocating the worms. For those who are interested in this phase of the problem, the articles by Stoll (8) and Stoll and Hausheer (9) on the dilution egg counting method may be referred to. This method is serviceable with nematode and trematode infestations, and probably with some cestodes. Certain modifications of this technic have been suggested by Chandler (10), Caldwell and Caldwell (11) and Hung (12).

Finally, a procedure which permits not only the determination of the presence of the given intestinal worms, but their approximate number and species, is the recovery of the worms themselves after vermicide by careful washing and sedimentation, or screening and sedimentation of the stools. Some of the less common parasites of man have been discovered by this technic, and when properly carried out, which requires considerable care, planning, and control of the patient, it is a most valuable procedure. Hitherto it has been applied primarily to the hookworm problem (see Darling, Barber and Hacker (13) Darling and Smillie (14), and Soper (15)) but it deserves more consideration in the study of other intestinal helminths.

It is not within the province of this chapter to go into specific descriptions of the various helminths under consideration, or even those which are recoverable by the worm count method just discussed. Species differentiation often calls for very careful technical examination. For morphological descriptions of the parasites, reference may be made to such texts as Castellani and Chalmers (16), Fantham, Stephens and Theobald (17), Manson-Bahr (18), Yorke and Maplestone (19), and Stiles and Hassal (20) as well as to the numerous special papers.

For the identification of the more usual ova found in human stools, the following key and Plate I will be of value. These are adapted from Cort—in Hegner, Cort and Root (21). The schistosome and hookworm ova have been included. While they do not represent infection conveyed by food, the eggs of

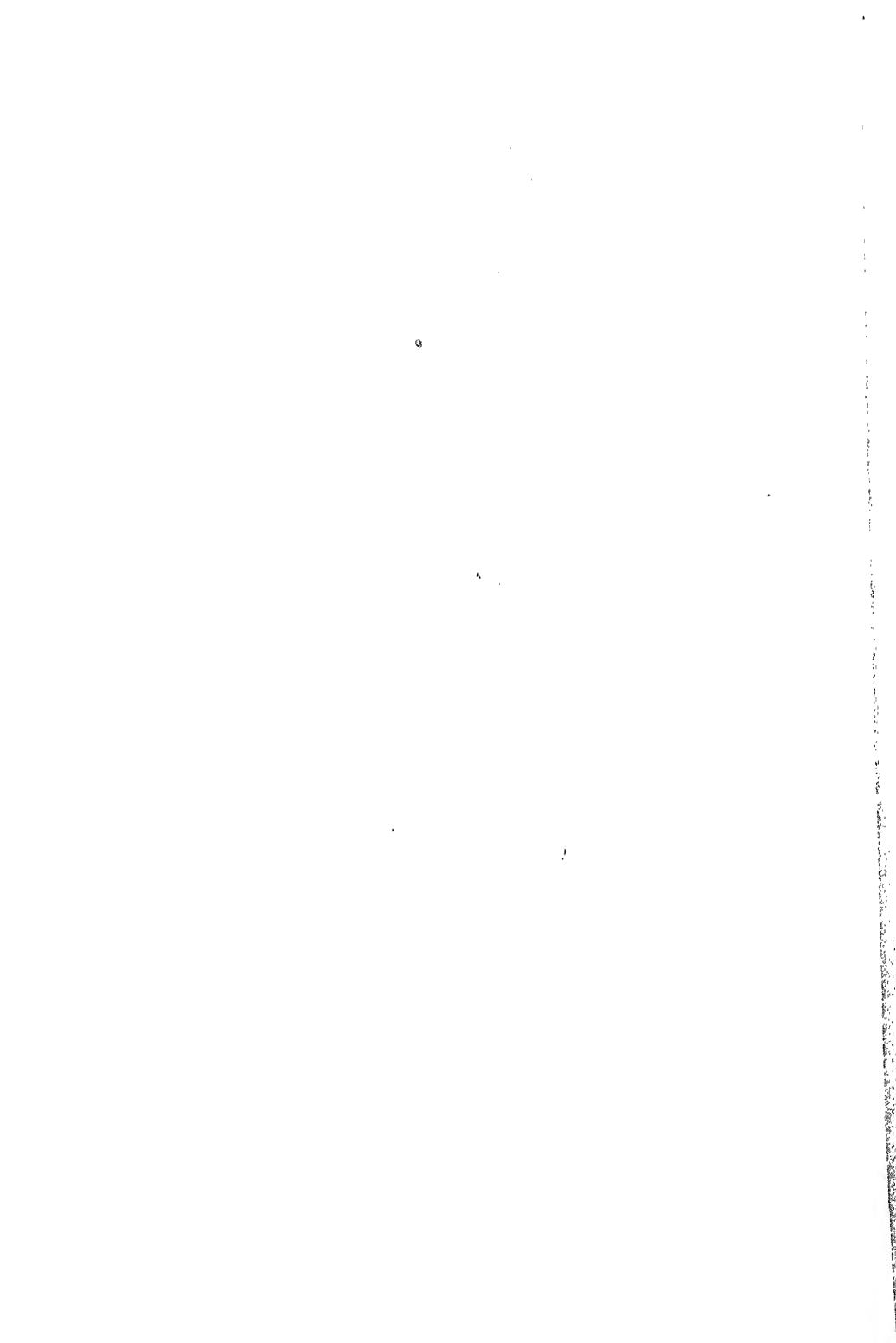
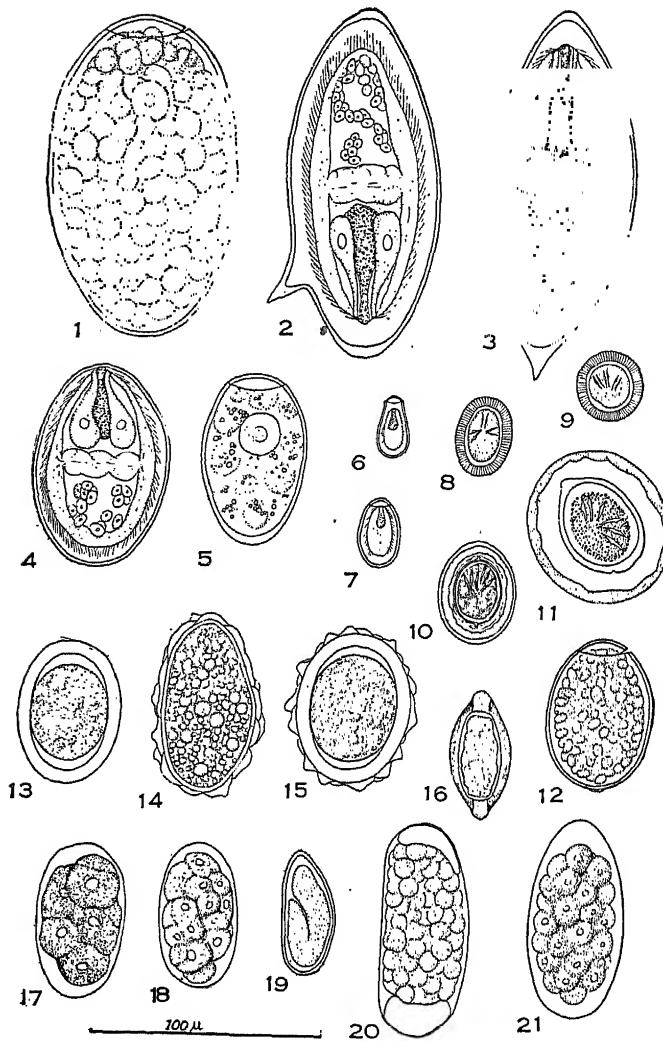


PLATE I



EGGS OF THE MOST IMPORTANT HELMINTHS

(1), *Fasciolopsis buski*; (2), *Schistosoma mansoni*; (3), *Schistosoma haematoalbum*; (4), *Schistosoma japonicum*; (5), *Paragonimus westermani*; (6), *Clonorchis sinensis*; (7), *Metagonimus yokogawai*; (8), *Taenia saginata*; (9), *Taenia solium*; (10), *Hymenolepis nana*; (11), *Hymenolepis diminuta*; (12), *Diphyllobothrium latum*; (13), *Ascaris lumbricoides* (egg without outer coating); (14), *Ascaris lumbricoides* (abnormal egg); (15), *Ascaris lumbricoides*; (16), *Trichuris trichiura*; (17) and (18), Hookworm eggs; (19), *Enterobius vermicularis* (*Oxyuris vermicularis*); (20), *Heterodera radicicola* (*Oxyuris incognita*); (21), *Trichostrongylus orientalis*. Adapted from Hegner, Cort and Root.

these forms, when encountered, need to be differentiated from those which are of direct concern to us in this chapter.

SPURIOUS PARASITISM

In the key will be found the description, and in Plate I the figure, of the egg of *Heterodera radicicola*. This form was reported by Kofoid and White (22) in 1919, as present in the stools of 427 out of approximately 140,000 American soldiers examined during the World War, and in the absence of any worms was designated *Oxyuris incognita*. Sandground (23), has since shown that this is really the egg of a plant nematode *Heterodera radicicola*, evidently ingested with imperfectly cleaned fresh vegetables, and uninjured in its intestinal passage. Since attention has been called to it this egg has been frequently reported in human stools. It serves as an excellent example of spurious parasitism.

KEY FOR IDENTIFICATION OF EGGS OF HUMAN HELMINTHS

The order of consideration of the more important parasites discussed here, in the different groups, follows in the main, that given in the recent paper by Stiles and Hassal (20). The nomenclature of some of the nematodes has been altered to follow Yorke and Maplestone (19), however.

A. Eggs in Sputum.

*Paragonimus westermani*² (Plate I, Fig. 5). Operculate: brownish or yellowish brown in color; contains fertilized ovum surrounded by yolk cells; 80 μ to 100 μ by 52 μ to 75 μ

B. Eggs in Feces.

I. Operculum present.

a. Eggs under 40 μ in length; contain a fully developed miracidium.

1. Operculum sharply defined with shell projecting slightly beyond its edge.

(a) *Opisthorchis felineus*.³ Size of egg 30 μ by 11 μ .

² Eggs of this form are also found in feces from swallowing of sputum by the patient.

³ It is difficult, if not impossible, in the present state of our knowledge, to distinguish these species by their eggs. Since their geographical distribution differs, the locality from which the patient comes will usually give a clue to the specific identity of the worms.

- (b) *Clonorchis sinensis*.³ (Plate I, Fig. 6.) Average size of egg, 29μ by 16μ .
- 2. Operculum not sharply defined, the shape being regularly oval.
 - (a) Egg brownish with thick shell.
Heterophyes heterophyes. Average size of eggs 30μ by 17μ .
 - (b) Egg yellowish with rather thin shell.
Metagonimus yokogawai. (Plate I, Fig. 7.) Average size of eggs 28μ by 16μ .
- b. Eggs over 50μ in length; do not contain a fully developed embryo.
 - 1. *Paragonimus westermani*.⁴ (Plate I, Fig. 5.) Size of egg 80μ to 100μ by 52μ to 75μ .
 - 2. *Fasciolopsis buski*. (Plate I, Fig. 1.) Size of egg 120μ to 130μ by 77μ to 80μ .
 - 3. *Gastrophiloides hominis*. Size of egg 150μ by 72μ .
 - 4. *Diphyllobothrium latum* (*Dibothriocephalus latus*). (Plate I, Fig. 12.) Size of egg 55μ to 76μ by 41μ to 56μ ; operculum small, not sharply defined. Shell thin, transparent, light straw color.

II. Operculum absent.

- a. Round or slightly oval, containing a six-hooked embryo; cestode eggs.
 - 1. With a thick radially striated inner shell or embryophore.
 - (a) *Taenia saginata* (Plate I, Fig. 8). Embryophore, ovoid, rusty brown, 35μ to 40μ in length by 20μ to 30μ in width.
 - (b) *Taenia solium* (Plate I, Fig. 9). Embryophore almost round; brown, 31μ to 36μ in diameter.
 - 2. With thin membranous inner shell.
 - (a) *Hymenolepis nana* (Plate I, Fig. 10). Oval or globular, with two distinct membranes; outer 30μ to 60μ in diameter; inner 16μ to 34μ , filiform projections at each pole of inner membrane.
 - (b) *Hymenolepis diminuta* (Plate I, Fig. 11). Round or oval; outer membrane 54μ to 86μ ; yellowish, may be striated; inner membrane 24μ to 40μ by 36μ .
- b. Oval, yellowish brown in color, containing a fully developed miracidium; trematode eggs.
 - 1. Large lateral spine present, 120μ to 140μ by 50μ to 60μ . *Schistosoma mansoni* (Plate I, Fig. 2).
 - 2. Only small rudimentary spine, if any present, 80μ to 85μ by 35μ to 40μ . *Schistosoma japonicum* (Plate I, Fig. 4).

³ The eggs of this species are found only occasionally in feces since in man they are usually expelled with the sputum.

- c. Shape, oval, considerably longer than wide; nematode eggs.
 - 1. Somewhat barrel shaped; with plugs at each end. *Trichuris trichiura* (Plate I, Fig. 16). Color of eggs dark brown; 50 μ to 57 μ by 23 μ ; ovum unsegmented.
 - 2. Thick transparent shell with an external albuminous coating which forms protuberances. *Ascaris lumbricoides* (Plate I, Figs. 13, 14, 15). Color of eggs brown; 50 μ to 70 μ by 40 μ to 50 μ ; ovum unsegmented.
 - 3. Asymmetrical, flattened on one side.
 - (a) *Enterobius vermicularis* (*Oxyuris vermicularis*) (Plate I, Fig. 19). Color transparent; contains tadpole-like embryo; size of egg 50 μ to 55 μ by 16 μ to 24 μ .
 - (b) *Heterodera radicicola* (*Oxyuris incognita*) (Plate I, Fig. 20). Oil globules at each end of egg; average size of egg 95 μ by 40 μ .
 - 4. Shell thin, transparent; embryo in four to many cell stages.
 - (a) *Trichostrongylus orientalis* (Plate I, Fig. 21). Ends somewhat pointed; size 75 μ to 90 μ by 39 μ to 47 μ .
 - (b) *Necator americanus*. Size 58 μ to 80 μ by 35 μ to 52 μ .
 - (c) *Ancylostoma duodenale* (Plate I, Figs. 17-18). Size 56 μ to 61 μ by 34 μ to 38 μ .

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